Access DB# _____

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Natalie Davis Examiner #: 78462 Date: 5-8-02
Art Unit: 1642 Phone Number 30 8-6410 Serial Number: 09/780586
Mail Box and Bldg/Room Location: _____ Results Format Preferred (circle): PAPER DISK E-MAIL
8E12 CM1 8B13

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): _____

_____

Earliest Priority Filing Date: _____

For Sequence Searches Only *Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please search claims 25-32 for a method of screening ~~compds~~ compounds for anti-cancer activity by contacting a cell with dysregulated c-MYC expression with a test compound & measuring CDK4 activity in the cell, where ~~is~~ no activity is indicative of anti-cancer activity.

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STAFF USE ONLY

Searcher: _____
Searcher Phone #: _____
Searcher Location: _____
Date Searcher Picked Up: 5-16-02
Date Completed: 5-20-02
Searcher Prep & Review Time: 15
Clerical Prep Time: _____
Online Time: 49

Point of Contact:
Alexandra Waclawiw
Technical Info. Specialist
CM1 6A02 Tel: 308-4491

Type of Search

NA Sequence (#) _____
AA Sequence (#) _____
Structure (#) _____
Bibliographic ✓
Litigation _____
Fulltext _____
Patent Family _____
Other _____

Vendors and cost where applicable

STN $394.00
Dialog _____
Questel/Orbit _____
Dr.Link _____
Lexis/Nexis _____
Sequence Systems _____
WWW/Internet _____
Other (specify) _____

pap 6
54-5
15
39
10
49

PTO-1590 (8-01)

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=> d his

     (FILE 'REGISTRY' ENTERED AT 07:39:03 ON 20 MAY 2002)
               DEL HIS Y
               E CDK4 KINASE/CN
L1             1 S E3

     FILE 'HCAPLUS' ENTERED AT 07:45:59 ON 20 MAY 2002
L2          1098 S L1
L3          1305 S CDK4 OR CDK 4 OR CYCLIN DEPENDENT KINASE (2W) 4
L4          7690 S C MYC OR CMYC
L5            76 S L4 AND L3
L6            21 S L4 (L) L3
L7        109919 S ANTICANCER# OR ANTITUMOR? OR ANTINEOPLAS?
L8         14416 S DRUG (L) SCREEN?
L9            12 S L5 AND L7
L10            5 S L8 AND L5
L11           13 S L9 OR L10
L12        43448 S BURKITT# OR NEUROBLASTOM? OR COLON CANCER? OR TRANSLOCAT? OR
L13            8 S L5 AND L12
L14           18 S L11 OR L13
L15           19 S L6 NOT L14
L16          443 S L3 (L) INHIBIT?
L17           16 S L5 AND L16
L18           12 S L17 NOT L14
L19        66174 S SCREEN?
L20            5 S L5 AND L19
L21           18 S L20 OR L14
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=> fil reg
FILE 'REGISTRY' ENTERED AT 07:52:31 ON 20 MAY 2002
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STRUCTURE FILE UPDATES:   16 MAY 2002  HIGHEST RN 418253-06-2
DICTIONARY FILE UPDATES:  16 MAY 2002  HIGHEST RN 418253-06-2

TSCA INFORMATION NOW CURRENT THROUGH July 7, 2001

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Calculated physical property data is now available.  See HELP PROPERTIES
for more information.  See STNote 27, Searching Properties in the CAS
Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d que l1
L1            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "CDK4 KINASE"/CN


=> d l1

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2002 ACS
RN   147014-97-9  REGISTRY
CN   Kinase (phosphorylating), protein p33CDK4 (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   Cdk4 kinase
CN   CDK4 protein kinase
CN   Cyclin-dependent kinase 4
CN   Cyclin-dependent kinase cdk4
CN   Cyclin-dependent protein kinase 4
CN   Gene CDK4 kinase
CN   p33cdk4 Kinase
CN   p33cdk4 Protein kinase
CN   p34cdk4 Protein kinase
CN   Protein kinase CDK4
CN   Protein p33cdk4 kinase
MF   Unspecified
CI   MAN
SR   CA
LC   STN Files:   BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CIN, EMBASE,
       PROMT, TOXCENTER, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
            1093 REFERENCES IN FILE CA (1967 TO DATE)
              31 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
            1098 REFERENCES IN FILE CAPLUS (1967 TO DATE)


=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 07:52:37 ON 20 MAY 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 20 May 2002 VOL 136 ISS 21
FILE LAST UPDATED: 19 May 2002 (20020519/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

CAS roles have been modified effective December 16, 2001. Please
check your SDI profiles to see if they need to be revised. For
information on CAS roles, enter HELP ROLES at an arrow prompt or use
the CAS Roles thesaurus (/RL field) in this file.
'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

=> d his l2-

(FILE 'HCAPLUS' ENTERED AT 07:45:59 ON 20 MAY 2002)

L2	1098	S	L1
L3	1305	S	CDK4 OR CDK 4 OR CYCLIN DEPENDENT KINASE (2W) 4
L4	7690	S	C MYC OR CMYC
L5	76	S	L4 AND L3
L6	21	S	L4 (L) L3
L7	109919	S	ANTICANCER# OR ANTITUMOR? OR ANTINEOPLAS?
L8	14416	S	DRUG (L) SCREEN?
L9	12	S	L5 AND L7
L10	5	S	L8 AND L5
L11	13	S	L9 OR L10
L12	43448	S	BURKITT# OR NEUROBLASTOM? OR COLON CANCER? OR TRANSLOCAT? OR
L13	8	S	L5 AND L12
L14	18	S	L11 OR L13
L15	19	S	L6 NOT L14
L16	443	S	L3 (L) INHIBIT?
L17	16	S	L5 AND L16
L18	12	S	L17 NOT L14
L19	66174	S	SCREEN?
L20	5	S	L5 AND L19
L21	18	S	L20 OR L14

FILE 'REGISTRY' ENTERED AT 07:52:31 ON 20 MAY 2002

FILE 'HCAPLUS' ENTERED AT 07:52:37 ON 20 MAY 2002

=> d .ca l18 1-12;d .ca l21 1-18

L18 ANSWER 1 OF 12 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:909683 HCAPLUS
TITLE: The functional genomic response of developing embryonic submandibular glands to NF-.kappa.B inhibition
AUTHOR(S): Melnick, Michael; Chen, Haiming; Zhou, Yan Min;

Jaskoll, Tina
CORPORATE SOURCE: Laboratory for Developmental Genetics, University of Southern California Los Angeles, CA, USA
SOURCE: BMC Developmental Biology [online computer file] (2001), 1, No pp. given
CODEN: BDBMA7; ISSN: 1471-213X
URL: http://www.biomedcentral.com/1471-213X/1/15
PUBLISHER: BioMed Central Ltd.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB The proper balance between epithelial cell proliferation, quiescence, and apoptosis during development is mediated by the specific temporal and spatial appearance of transcription factors, growth factors, cytokines, caspases, etc. Since the authors' prior studies suggest the importance of transcription factor NF-.kappa.B during embryonic submandibular salivary gland (SMG) development, we attempted to delineate the emergent dynamics of a cognate signaling network by studying the mol. patterns and phenotypic outcomes of interrupted NF-.kappa.B signaling in embryonic SMG explants. SN50-mediated inhibition of NF-.kappa.B nuclear translocation in E15 SMG explants cultured for 2 days results in a highly significant increase in apoptosis and decrease in cell proliferation. Probabilistic Neural Network (PNN) analyses of transcriptomic and proteomic assays identify specific transcripts and proteins with altered expression that best discriminate control from SN50-treated SMGs. These include PCNA, GR, BMP1, BMP3b, Chk1, Caspase 6, E2F1, c-Raf, ERK1/2 and JNK-1, as well as several others of lesser importance. Increased expression of signaling pathway components is not necessarily probative of pathway activity; however, as confirmation we found a significant increase in activated (phosphorylated/cleaved) ERK 1/2, Caspase 3, and PARP in SN50-treated explants. This increased activity of proapoptotic (caspase3/PARP) and compensatory antiapoptotic (ERK1/2) pathways is consistent with the dramatic cell death seen in SN50-treated SMGs. This morphol. and functional genomic analyses indicate that the primary and secondary effects of NF-.kappa.B-mediated transcription are crit. to embryonic SMG developmental homeostasis. Relative to understanding complex genetic networks and organogenesis, these results illustrate the importance of evaluating the gene, protein, and activated protein expression of multiple components from multiple pathways within broad functional categories.
CC 13-3 (Mammalian Biochemistry)
Section cross-reference(s): 3
IT INDEXING IN PROGRESS
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**Cdk4**; functional genomic response of developing embryonic submandibular glands to NF-.kappa.B **inhibition**)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**c-myc**; functional genomic response of developing embryonic submandibular glands to NF-.kappa.B inhibition)
IT 147014-97-9, **Cyclin dependent kinase 4**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**4**; functional genomic response of developing embryonic submandibular glands to NF-.kappa.B **inhibition**)
REFERENCE COUNT: 108 THERE ARE 108 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 2 OF 12 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:863551 HCAPLUS

DOCUMENT NUMBER: 136:18866
TITLE: Transgenic mice containing an oncogene or a tumor suppressor gene operably linked to urothelium-specific uroplakin promoter as animal models for human bladder cancer
INVENTOR(S): Wu, Xue-ru; Sun, Tung-tien
PATENT ASSIGNEE(S): New York University, USA
SOURCE: U.S., 32 pp., Cont.-in-part of U.S. Ser. No. 969,315.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6323390	B1	20011127	US 1998-83541	19980522
US 5824543	A	19981020	US 1995-464961	19950605
US 6001646	A	19991214	US 1997-907800	19970808
US 6339183	B1	20020115	US 1997-969315	19971113
WO 9925810	A1	19990527	WO 1998-US24038	19981112

W: CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRIORITY APPLN. INFO.:
US 1995-464961 A2 19950605
US 1997-907800 A2 19970808
US 1997-969315 A2 19971113
US 1998-83541 A 19980522

AB A transgenic mammal, preferably a mouse, contg. an oncogene or a tumor suppressor gene operably linked to a urothelium-specific promoter in its germ cells and somatic cells, serves as an animal model system for human bladder cancer. This invention specifically provides transgenic mice whose germ and somatic cells contain a transgene in which an oncogene (SV40 large T antigen and H-ras), or a tumor suppressor gene (p53), is operably linked to the urothelium-specific uroplakin II promoter. The invention also demonstrated: (1) transgenic mice expressing uroplakin II-SV40 large T antigen transgene develop carcinoma in situ and invasive cancers of the bladder, and (2) transgenic mice contg. uroplakin II-H-ras transgene induced urothelial hyperplasia and superficial papillary tumor of the bladder.

IC ICM C12N015-09
ICS C12N015-63; C12N015-00; C12N005-00
NCL 800018000
CC 14-1 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 3
IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(**c-myc**, functionally diactivated; transgenic mice contg. oncogene or tumor suppressor gene operably linked to urothelium-specific uroplakin promoter as animal models for human bladder cancer)
IT Gene, animal
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(for protein p16, **inhibitor** of **cyclin-dependent kinase 4**, functionally diactivated; transgenic mice contg. oncogene or tumor suppressor gene operably linked to urothelium-specific uroplakin promoter as animal models for human bladder cancer)

IT Gene, animal
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(oncogene, H-ras, Neu/erbB-2 and **c-myc**; transgenic mice contg. oncogene or tumor suppressor gene operably linked to urothelium-specific uroplakin promoter as animal models for human bladder cancer)
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:597121 HCAPLUS
DOCUMENT NUMBER: 135:286242
TITLE: P21Cip1 induced by Raf is associated with increased **Cdk4** activity in hematopoietic cells
AUTHOR(S): Chang, Fumin; McCubrey, James A.
CORPORATE SOURCE: Department of Microbiology and Immunology, Brody School of Medicine, East Carolina University, Greenville, NC, 27858, USA
SOURCE: Oncogene (2001), 20(32), 4354-4364
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To investigate the functions of the different Raf genes in hematopoietic cell proliferation, the capacities of .beta.-estradiol-regulated .DELTA.Raf:ER genes to induce cell cycle regulatory gene expression and cell cycle progression in FDC-P1 cells were examd. Raf activation increased the expression of Cdk2, Cdk4, cyclin A, cyclin D, cyclin E, p21Cip1 and c-Myc and decreased the expression of p27Kip1 which are assocd. with G1 progression. However only the cell clones with moderate Raf activation, i.e. FD/.DELTA.Raf-1:ER and FD/.DELTA.A-Raf:ER, successfully underwent cell proliferation. The cell clones with the highest .DELTA.Raf activity, FD/.DELTA.B-Raf:ER, underwent apoptosis before cell proliferation. P21Cip1 induced by Raf activation specifically bound with Cdk4/cyclin D complexes but not Cdk2/cyclin E complexes and this binding was assocd. with the increased Cdk4 activity. However, no binding of p27Kip1 with either Cdk2/cyclin E or Cdk4/cyclin D was obsd. Thus Raf-mediated growth was assocd. with elevated p21Cip1 expression, which may specifically bind with and activate Cdk4/cyclin D complexes and with decreased p27Kip1 expression.
CC 13-5 (Mammalian Biochemistry)
ST p21CIP1 Raf kinase **Cdk4** cyclin D hematopoietic cell proliferation; Cdk2 kinase cyclin A myc transcription factor cell cycle; p27KIP1 cyclin E MEK1 kinase Raf signaling hematopoietic cell
IT Molecular association
(P21Cip1 - **Cdk4**/cyclin D complex; Raf-induced P21Cip1 is assocd. with increased **Cdk4** activity and **Cdk4**/cyclin D complexes in hematopoietic cells)
IT Cell cycle
Cell proliferation
Hematopoietic precursor cell
Signal transduction, biological
(Raf-induced P21Cip1 is assocd. with increased **Cdk4** activity and **Cdk4**/cyclin D complexes in hematopoietic cells)
IT Transcription factors
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(**c-myc**; effect of Raf activation on cell cycle

regulatory protein expression)

IT Cyclin dependent kinase **inhibitors**
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(p21CIP1/WAF1; Raf-induced P21Cip1 is assocd. with increased **Cdk4** activity and **Cdk4**/cyclin D complexes in hematopoietic cells)

IT 139691-76-2, Raf-1 kinase 144697-16-5, B-Raf kinase 147014-97-9, protein kinase **Cdk4** 150027-19-3, A-Raf kinase
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(Raf-induced P21Cip1 is assocd. with increased **Cdk4** activity and **Cdk4**/cyclin D complexes in hematopoietic cells)

IT 149371-07-3, cyclin D/**Cdk4** kinase
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Raf-induced P21Cip1 is assocd. with increased **Cdk4** activity and **Cdk4**/cyclin D complexes in hematopoietic cells)

REFERENCE COUNT: 99 THERE ARE 99 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:570337 HCAPLUS
DOCUMENT NUMBER: 135:237069
TITLE: Inhibitory effects of 1.alpha.,25-dihydroxyvitamin D3 on the G1-S phase-controlling machinery
AUTHOR(S): Jensen, Simon Skjode; Madsen, Mogens Winkel; Lukas, Jiri; Binderup, Lise; Bartek, Jiri
CORPORATE SOURCE: Institute of Cancer Biology, The Danish Cancer Society, Copenhagen, DK-2100, Den.
SOURCE: Molecular Endocrinology (2001), 15(8), 1370-1380
CODEN: MOENEN; ISSN: 0888-8809
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The nuclear hormone 1.alpha.,25-dihydroxyvitamin D3 induces cell cycle arrest, differentiation, or apoptosis depending on target cell type and state. Although the antiproliferative effect of 1.alpha.,25-dihydroxyvitamin D3 has been known for years, the mol. basis of the cell cycle blockade by 1.alpha.,25-dihydroxyvitamin D3 remains largely unknown. Here the authors have investigated the mechanisms underlying the G1 arrest induced upon 1.alpha.,25-dihydroxyvitamin D3 treatment of the human breast cancer cell line MCF-7. Twenty-four-hour exposure of exponentially growing MCF-7 cells to 1.alpha.,25-dihydroxyvitamin D3 impeded proliferation by preventing S phase entry, an effect that correlated with appearance of the growth-suppressing, hypophosphorylated form of the retinoblastoma protein (pRb), and modulation of cyclin-dependent kinase (cdk) activities of cdk-4, -6, and -2. Time course immunochem. and biochem. analyses of the cellular and mol. effects of 1.alpha.,25-dihydroxyvitamin D3 treatment for up to 6 d revealed a dynamic chain of events, preventing activation of cyclin D1/cdk4, and loss of cyclin D3, which collectively lead to repression of the E2F transcription factors and thus neg. affected cyclin A protein expression. While the obsd. 10-fold inhibition of cyclin D1/cdk 4-assocd. kinase activity appeared independent of cdk inhibitors, the activity of cdk 2 decreased about 20-fold, reflecting joint effects of the lower abundance of its cyclin partners and a significant increase of the cdk inhibitor p21CIP1/WAF1, which blocked

the remaining cyclin A(E)/cdk 2 complexes. Together with a rapid down-modulation of the c-Myc oncoprotein in response to 1.alpha.,25-dihydroxyvitamin D3, these results demonstrate that 1.alpha.,25-dihydroxyvitamin D3 inhibits cell proliferation by targeting several key regulators governing the G1/S transition.

CC 2-10 (Mammalian Hormones)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**c-myc**; dihydroxyvitamin D3 inhibition of G1-S phase-controlling machinery in antiproliferative effect)

IT 141349-86-2, cdk-2 kinase 141349-86-2D, cdk 2 kinase, complexes with cyclin A 147014-97-9, **cdk-4** kinase 303014-92-8
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(dihydroxyvitamin D3 **inhibition** of G1-S phase-controlling machinery in antiproliferative effect)

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:603871 HCAPLUS
DOCUMENT NUMBER: 133:318457
TITLE: Identification of a possible association between carbon tetrachloride-induced hepatotoxicity and interleukin-8 expression
AUTHOR(S): Holden, Peter R.; James, Neil H.; Brooks, A. Nigel; Roberts, Ruth A.; Kimber, Ian; Pennie, William D.
CORPORATE SOURCE: Zeneca Central Toxicology Laboratory, Macclesfield, SK10 4TJ, UK
SOURCE: Journal of Biochemical and Molecular Toxicology (2000), 14(5), 283-290
CODEN: JBMTFQ; ISSN: 1095-6670
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Hepatotoxicants can elicit liver damage by various mechanisms that can result in cell necrosis and death. The changes induced by these compds. can vary from gross alterations in DNA repair mechanisms, protein synthesis, and apoptosis, to more discrete changes in oxidative damage and lipid peroxidn. However, little is known of the changes in gene expression that are fundamental to the mechanisms of hepatotoxicity. The authors have used DNA microarray technol. to identify gene transcription assocd. with the toxicity caused by the hepatotoxicant carbon tetrachloride. Labeled poly A+ RNA from cultured human hepatoma cells (HepG2) exposed to carbon tetrachloride for 8 h was hybridized to a human microarray filter. The authors found that 47 different genes were either upregulated or down-regulated more than 2-fold by the hepatotoxicant compared with DMF, a chem. that does not cause liver cell damage. The proinflammatory cytokine interleukin-8 (IL-8) was upregulated over 7-fold compared with control on the array, and this was subsequently confirmed at 1 h and 8 h by Northern blot analyses. The authors also found that carbon tetrachloride caused a time-dependent increase in interleukin-8 protein release in HepG2 cells, which was parallelled by a decrease in cell viability. These data demonstrate that carbon tetrachloride causes a rapid increase in IL-8 mRNA expression in HepG2 cells and that this increase correlates with a later and significant increase in the levels of interleukin-8 protein. These results illustrate the potential of microarray technol. in the identification of novel gene changes assocd. with toxic processes.

CC 4-6 (Toxicology)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**c-myc**; carbon tetrachloride-induced hepatotoxicity and interleukin-8 expression)
IT 147014-97-9, **Cdk4** kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitor** p16-INK4; carbon tetrachloride-induced hepatotoxicity and interleukin-8 expression)
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 6 OF 12 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:392018 HCAPLUS
DOCUMENT NUMBER: 133:100012
TITLE: Stem cell factor inhibits erythroid differentiation by modulating the activity of G1-cyclin-dependent kinase complexes: a role for p27 in erythroid differentiation coupled G1 arrest
AUTHOR(S): Tamir, Ami; Petrocelli, Teresa; Stetler, Kendra; Chu, Wendy; Howard, Jeff; Croix, Brad St.; Slingerland, Joyce; Ben-David, Yaacov
CORPORATE SOURCE: Department of Medical Biophysics, University of Toronto, Can.
SOURCE: Cell Growth & Differentiation (2000), 11(5), 269-277
CODEN: CGDIE7; ISSN: 1044-9523
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Terminal erythroid differentiation is accompanied by decreased expression of c-Kit and decreased proliferation of erythroid progenitor cells. Using a newly established erythroleukemia cell line HB60-5, which proliferates in response to erythropoietin (Epo) and stem cell factor (SCF) and differentiates when stimulated with Epo alone, the authors characterized several events assocd. with the cell cycle during erythroid differentiation. Forty-eight h after SCF withdrawal and Epo stimulation, there was strong inhibition of cyclin-dependent kinase (cdk) 4 and cdk6 activities, assocd. with an increase in the binding of p27 and p15 to cdk6. A significant increase in the binding of p27 to cyclin E- and cyclin A-assocd. cdk2 correlated with the inhibition of these kinases. In addn., the expression of c-Myc and its downstream transcriptional target Cdc25A were found to be down-regulated during Epo-induced terminal differentiation of HB60-5 cells. The loss of Cdc25A was assocd. with an increase in the phosphotyrosylation of cyclin E-assocd. cdk2, which may contribute to cell cycle arrest during differentiation. Although overexpression of p27 in HB60-5 cells caused G1 arrest, it did not promote terminal erythroid differentiation. Thus, the cell cycle arrest that involves p27 is part of a broader mol. program during HB60-5 erythroid differentiation. Moreover, the authors suggest that SCF stimulation of erythroblasts, in addn. to inhibiting erythroid differentiation, activates parallel or sequential signals responsible for maintaining cyclin/cdk activity.
CC 2-10 (Mammalian Hormones)
Section cross-reference(s): 13
IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**c-myc**; stem cell factor inhibits erythroid differentiation by modulating activity of G1-cyclin-dependent kinase complexes in relation to role for p27 in erythroid differentiation

coupled G1 arrest)
IT 140208-22-6, Cdc25A phosphatase 141349-86-2, Kinase (phosphorylating), gene cdk2 protein 141349-86-2 147014-97-9, **Cdk4** kinase 154907-66-1, Cdk6 kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(stem cell factor **inhibits** erythroid differentiation by modulating activity of G1-cyclin-dependent kinase complexes in relation to role for p27 in erythroid differentiation coupled G1 arrest)
REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 7 OF 12 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:404322 HCAPLUS
DOCUMENT NUMBER: 131:168326
TITLE: **c-myc** regulates cyclin D-**Cdk4** and -Cdk6 activity but affects cell cycle progression at multiple independent points
AUTHOR(S): Mateyak, Maria K.; Obaya, Alvaro J.; Sedivy, John M.
CORPORATE SOURCE: Department of Molecular Biology, Cell Biology, and Biochemistry, Brown University, Providence, RI, 02912, USA
SOURCE: Molecular and Cellular Biology (1999), 19(7), 4672-4683
CODEN: MCEBD4; ISSN: 0270-7306
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB C-myc is a cellular proto-oncogene assocd. with a variety of human cancers and is strongly implicated in the control of cellular proliferation, programmed cell death, and differentiation. We have previously reported the first isolation of a c-myc-null cell line. Loss of c-Myc causes a profound growth defect manifested by the lengthening of both the G1 and G2 phases of the cell cycle. To gain a clearer understanding of the role of c-Myc in cellular proliferation, we have performed a comprehensive anal. of the components that regulate cell cycle progression. The largest defect obsd. in c-myc-/- cells is a 12-fold redn. in the activity of cyclin D1-Cdk4 and -Cdk6 complexes during the G0-to-S transition. Downstream events, such as activation of cyclin E-Cdk2 and cyclin A-Cdk2 complexes, are delayed and reduced in magnitude. However, it is clear that c-Myc affects the cell cycle at multiple independent points, because restoration of the Cdk4 and -6 defect does not significantly increase growth rate. In exponentially cycling cells the absence of c-Myc reduces coordinately the activities of all cyclin-cyclin-dependent kinase complexes. An anal. of cyclin-dependent kinase complex regulators revealed increased expression of p27KIP1 and decreased expression of Cdk7 in c-myc-/- cells. We propose that c-Myc functions as a crucial link in the coordinate adjustment of growth rate to environmental conditions.
CC 13-6 (Mammalian Biochemistry)
ST **cmyc** cyclin cdk kinase cell cycle
IT Cyclins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(-cyclin-dependent kinase complexes; **c-myc** regulates cyclin D-**Cdk4** and -Cdk6 activity but affects cell cycle progression at multiple independent points)
IT Interphase (cell cycle)
(G0-to-S transition; **c-myc** regulates cyclin D-**Cdk4** and -Cdk6 activity but affects cell cycle progression at multiple independent points)

IT Interphase (cell cycle)
(G1-phase; **c-myc** regulates cyclin D-**Cdk4** and -Cdk6 activity but affects cell cycle progression at multiple independent points)
IT Interphase (cell cycle)
(G2-phase; **c-myc** regulates cyclin D-**Cdk4** and -Cdk6 activity but affects cell cycle progression at multiple independent points)
IT Cell cycle
Cell proliferation
(**c-myc** regulates cyclin D-**Cdk4** and -Cdk6 activity but affects cell cycle progression at multiple independent points)
IT Transcription factors
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**c-myc**; **c-myc** regulates cyclin D-**Cdk4** and -Cdk6 activity but affects cell cycle progression at multiple independent points)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**c-myc**; **c-myc** regulates cyclin D-**Cdk4** and -Cdk6 activity but affects cell cycle progression at multiple independent points)
IT Cyclin dependent kinase **inhibitors**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(p27KIP1; **c-myc** regulates cyclin D-**Cdk4** and -Cdk6 activity but affects cell cycle progression at multiple independent points)
IT 142805-58-1, Cdk7 kinase 146279-88-1, Cyclin A-Cdk2 kinase 146279-89-2, Cyclin E-Cdk2 kinase 150428-23-2D, Cyclin-dependent kinase, complexes with cyclins 166433-52-9 166433-53-0, Cyclin D1-**Cdk4** kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**c-myc** regulates cyclin D-**Cdk4** and -Cdk6 activity but affects cell cycle progression at multiple independent points)
REFERENCE COUNT: 123 THERE ARE 123 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 8 OF 12 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:350736 HCAPLUS
DOCUMENT NUMBER: 131:3862
TITLE: Production of transgenic mice containing an oncogene or a tumor suppressor gene operably linked to urothelium-specific uroplakin II promoter and their use as animal models for human bladder cancer
INVENTOR(S): Wu, Xue-ru; Sun, Tung-tien
PATENT ASSIGNEE(S): New York University, USA
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9925810	A1	19990527	WO 1998-US24038	19981112
W: CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 6339183	B1	20020115	US 1997-969315	19971113
US 6323390	B1	20011127	US 1998-83541	19980522

PRIORITY APPLN. INFO.: US 1997-969315 A 19971113
US 1998-83541 A 19980522
US 1995-464961 A2 19950605
US 1997-907800 A2 19970808

AB A transgenic non-human mammal, which is preferably a mouse, contg. an oncogene or a tumor suppressor gene operably linked to a urothelium-specific promoter in its germ cells and somatic cells, serves as an animal model system for human bladder cancer. This invention specifically provides transgenic mice whose germ and somatic cells contain a transgene in which an oncogene (SV40 large T antigen and H-ras), or a tumor suppressor gene (p53), is operably linked to the urothelium-specific uroplakin II promoter. The invention also demonstrated: (1) transgenic mice expressing uroplakin II-SV40 large T antigen transgene develop carcinoma in situ and invasive cancers of the bladder, and (2) transgenic mice contg. uroplakin II-H-ras transgene induced urothelial hyperplasia and superficial papillary tumor of the bladder.

IC ICM C12N005-00
ICS C12N015-00; C12N015-09; C12N015-63

CC 14-1 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 3

IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(**c-myc**; prodn. of transgenic mice contg. an oncogene or a tumor suppressor gene operably linked to urothelium-specific uroplakin II promoter and use as animal models for human bladder cancer)

IT Gene, animal
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(for protein p16, **inhibitor** of **cyclin-dependent kinase 4**; prodn. of transgenic mice contg. an oncogene or a tumor suppressor gene operably linked to urothelium-specific uroplakin II promoter and use as animal models for human bladder cancer)

IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(oncogene, SV40 large T antigen, H-ras, Neu/erbB-2 and **c-myc**; prodn. of transgenic mice contg. an oncogene or a tumor suppressor gene operably linked to urothelium-specific uroplakin II promoter and use as animal models for human bladder cancer)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 9 OF 12 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:2370 HCAPLUS
DOCUMENT NUMBER: 130:166142
TITLE: Inhibition of G1 cyclin-dependent kinase activity in cell density-dependent growth arrest in human fibroblasts
AUTHOR(S): Afrakhte, Mozhgan; Heldin, Nils-Erik; Westermark,

Bengt
CORPORATE SOURCE: Department of Genetics and Pathology, Unit of Pathology, University Hospital, Uppsala, S-751 85, Swed.
SOURCE: Cell Growth & Differentiation (1998), 9(12), 983-988
CODEN: CGDIE7; ISSN: 1044-9523
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The growth of normal fibroblasts in culture ceases as the cells reach satn. d. Although cells in dense cultures express functionally active growth factor receptors, they are essentially refractory to the mitogenic activity of growth factors. Northern blot anal. revealed that immediate early genes, c-myc, c-fos and c-jun are induced by mitogen in dense cultures. However, these cells fail to express the late G1 genes such as E2F-1, cdc25A, and cyclin A in response to mitogen stimulation. Furthermore, because pRb-phosphorylation is a key event in G1 progression, here, we show that in dense cultures, pRb remains in its active (hypophosphorylated) form after stimulation by mitogens. We also show that the kinase activity of cyclin-dependent kinases that are indispensable for the phosphorylation of pRb in late G1 phase was decreased on increasing cell d. The reduced kinase activity may be caused by the obsd. increase in cyclin-dependent kinase inhibitors and the redn. of cdc25A expression in dense cells.

CC 13-6 (Mammalian Biochemistry)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**c-myc**, induced in dense cell cultures; inhibition of G1 cyclin-dependent kinase activity in cell d.-dependent growth arrest in human fibroblasts)

IT 141349-86-2, Cyclin-dependent kinase 2 147014-97-9, **Cyclin-dependent kinase 4** 154907-66-1, Cyclin-dependent kinase 6
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**inhibition** of G1 cyclin-dependent kinase activity in cell d.-dependent growth arrest in human fibroblasts)

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 10 OF 12 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:749222 HCAPLUS
DOCUMENT NUMBER: 128:59860
TITLE: Cyclic AMP negatively controls **c-myc** transcription and G1 cell cycle progression in p210 BCR-ABL transformed cells: **inhibitory** activity exerted through cyclin D1 and **cdk4**
AUTHOR(S): Williamson, E. A.; Burgess, G. S.; Eder, P.; Litz-Jackson, S.; Boswell, H. Scott
CORPORATE SOURCE: Walther Oncology Center, Indiana University School of Medicine, Indianapolis, IN, USA
SOURCE: Leukemia (1997), 11(1), 73-85
CODEN: LEUKED; ISSN: 0887-6924
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Raised intracellular cAMP has been demonstrated to exert an antiproliferative effect in myeloid cells. How the anti-proliferative activity of cAMP is exerted in p210 BCR-ABL transformed myeloid cells was

the subject of this investigation. It was hypothesized that cyclin dependent kinase 4, cdk4, might be a crit. target enzyme to affect the related events of c-myc transcription and progression through G1 phase of the cell cycle within cells transformed by p210 BCR-ABL, and further, that cdk4 might be downregulated by cAMP to inhibit proliferation. In order to investigate the regulatory role of cdk4, synchronized cells were studied. In p210 BCR-ABL transformed cells transiting early G1 phase, treatment with a cAMP analog led to inhibition of cyclin D1 synthesis, and marked redn. of cdk4 kinase activity. Within cells in which cdk4 was inhibited by cAMP, there was augmented interaction of E2F1 with the retinoblastoma protein, pRb in a nuclear matrix-assocd. cell fraction. As a result of E2F1 sequestration, raised intracellular cAMP was found to inhibit c-myc transcription in p210 BCR-ABL transformed myeloid cells synchronously transiting the early G1 phase of the cell cycle. A target of this transcriptional suppression exerted by cAMP was the E2F site of the c-myc P2 promoter. On the other hand, cyclin D1 content was not reduced by cAMP in these cells when it was applied at a later cell cycle stage at the interface between G1 and S. Corresponding to lack of cyclin D1 inhibition in these later G1-to-S phase cells, cdk4 activity was only modestly suppressed, and c-myc mRNA expression was also inhibited to a lesser degree. These studies show that Rb interaction with E2F1 is regulated by cdk4 and cyclin D1 within p210 BCR-ABL transformed leukemia cells in early G1 phase of the cell cycle. In this context, both cyclin D1 and cdk4 are subject to the level of intracellular cAMP. This interaction between Rb and E2F1, which is subject to the level of cAMP, is crit. to transcriptional control of c-myc. Further, pRb regulation of E2F activity affects cellular potential for G1-S phase transition in p210 BCR-ABL transformed myeloid cells, in part, via its effect on c-myc transcription.

CC 13-6 (Mammalian Biochemistry)
Section cross-reference(s): 14

ST cAMP **cmyc** transcription cell cycle myeloid; cyclin D1 **cdk4** cAMP cell cycle; antiproliferative effect hematopoietic transformation cAMP myeloid; leukemia antiproliferative effect cAMP myeloid cell

IT E2F (gene E2 promoter-specific factor)
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(E2F1; cAMP neg. controls **c-myc** transcription in p210 BCR-ABL transformed cells in relation to complex formation between pRb and E2F1)

IT Interphase (cell cycle)
(G1/S; cAMP neg. controls **c-myc** transcription and G1 cell cycle progression in p210 BCR-ABL transformed cells through cyclin D1 and **cdk4** pathway)

IT Phosphoproteins
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(P210bcr-c-abl; cAMP neg. controls **c-myc** transcription and G1 cell cycle progression in p210 BCR-ABL transformed cells through cyclin D1 and **cdk4** pathway)

IT Phosphorylation (biological)
(cAMP **inhibits cdk4** phosphorylation of pRb in p210 BCR-ABL transformed cells entering G1)

IT Rb protein
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(cAMP **inhibits cdk4** phosphorylation of pRb in p210 BCR-ABL transformed cells entering G1)

IT Cell cycle
G1 phase
Myeloid precursor cell
S phase

Transformation (neoplastic)
(cAMP neg. controls **c-myc** transcription and G1 cell cycle progression in p210 BCR-ABL transformed cells through cyclin D1 and **cdk4** pathway)

IT Cyclin D1
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(cAMP neg. controls **c-myc** transcription and G1 cell cycle progression in p210 BCR-ABL transformed cells through cyclin D1 and **cdk4** pathway)

IT **c-myc** gene (animal)
mRNA
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(cAMP-mediated delay of G1 population growth with **c-myc** mRNA inhibition in p210 BCR-ABL transformed cells)

IT 60-92-4, CAMP
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(cAMP neg. controls **c-myc** transcription and G1 cell cycle progression in p210 BCR-ABL transformed cells through cyclin D1 and **cdk4** pathway)

IT 147014-97-9, **Cdk4** kinase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(cAMP neg. controls **c-myc** transcription and G1 cell cycle progression in p210 BCR-ABL transformed cells through cyclin D1 and **cdk4** pathway)

L18 ANSWER 11 OF 12 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:667865 HCAPLUS
DOCUMENT NUMBER: 127:326710
TITLE: 17.beta.-Estradiol-enhanced growth inhibition of MDA-MB-468 cells stably transfected with the estrogen receptor: cell cycle effects
AUTHOR(S): Wang, Weili; Smith, Roger, III; Burghardt, Robert; Safe, Stephen H.
CORPORATE SOURCE: Depts. Vet. Physiol. and Pharmacology and Biochem. and Biophysics, Texas A&M Univ., College Station, TX, 77843-4466, USA
SOURCE: Mol. Cell. Endocrinol. (1997), 133(1), 49-62
CODEN: MCEND6; ISSN: 0303-7207
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Estrogen receptor (ER)-neg. MDA-MB-468 human breast cancer cells were stably transfected with wild-type human ER and utilized as a model for investigating estrogen- and aryl hydrocarbon (Ah)-responsiveness. Treatment of the stably transfected cells with 10 nM 17.beta.-estradiol (E2) resulted in a significant inhibition (>60%) of cell proliferation and DNA synthesis, which was blocked by 10-7 M ICI 182780. Anal. by flow cytometry indicated that treatment with E2 increased the percentage of cells in G0/G1 (from 68.8 to 89.4) and decreased cells in S (from 18.4 to 3.4) and G2/M (from 12.8 to 7.2) phases of the cell cycle. The effects of E2 on the major cyclins, cyclin-dependent kinases and cyclin-dependent kinase inhibitors, retinoblastoma protein (RB), E2F-1, and cyclin-dependent kinase activities were also investigated in the stably transfected MDA-MB-468 cells. The results demonstrated that the growth inhibitory effects of 10-8 M E2 in ER stably transfected MDA-MB-468 cells were assocd. with modulation of several factors required for cell cycle progression and DNA synthesis, including significant induction of the cyclin-dependent kinase inhibitor p21cip-1 (>4-fold increase after 12 h) and decreased E2F1 and PCNA protein levels. These results show that the

growth-inhibitory effects of E2 in the stably transfected cells were due to multiple factors which result in growth arrest in G0/G1 and inhibition of DNA synthesis.

CC 2-4 (Mammalian Hormones)
Section cross-reference(s): 14

IT Cyclin A
Cyclin D1
Cyclins E
Estrogen receptors
Proliferating cell nuclear antigen
c-fos gene (animal)
c-jun gene (animal)
c-myc gene (animal)
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(cell cycle effects in estradiol-enhanced growth inhibition of MDA-MB-468 cells stably transfected with estrogen receptor)

IT 141349-86-2, Cdk2 kinase 147014-97-9, **Cdk4** kinase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(cell cycle effects in estradiol-enhanced growth **inhibition** of MDA-MB-468 cells stably transfected with estrogen receptor)

L18 ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:809565 HCAPLUS
DOCUMENT NUMBER: 123:218633
TITLE: **c-Myc** and cyclin D3 (CcnD3) genes are independent targets for glucocorticoid inhibition of lymphoid cell proliferation
AUTHOR(S): Rhee, Kunsoo; Bresnahan, Wade; Hirai, Aki; Hirai, Masashi; Thompson, E. Aubrey
CORPORATE SOURCE: Dep. Human Biological Chem., Genetics, Univ. Texas Med. Branch, Galveston, TX, 77550-0645, USA
SOURCE: Cancer Res. (1995), 55(18), 4188-95
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Glucocorticoids inhibit the expression of crit. cell cycle-regulatory genes. The G1 cyclin gene CcnD3, which encodes cyclin D3, is inhibited by dexamethasone in P1798 murine T lymphoma cells. Glucocorticoids also inhibit expression of the catalytic partner of cyclin of cyclin D3, Cdk4. Inhibition of these two genes results in a decrease in the ability to phosphorylate the Rb-1 tumor suppressor gene product. Stable transformation with SV40 T antigen expression vectors prevents glucocorticoid-mediated cell cycle arrest, which is consistent with the conclusion that glucocorticoids inhibit Rb-1 phosphorylation. Overexpression of cyclin D3 suffices to restore Rb-kinase activity in glucocorticoid-treated cells. Nevertheless, overexpression of cyclin D3 does not prevent glucocorticoid inhibition of cell proliferation. Cells transformed with Cdk4 expression vectors, with or without cyclin D3 expression vectors, also undergo G0 arrest in the presence of dexamethasone. Glucocorticoids inhibit c-Myc expression in lymphoid cells, and transient expression of c-Myc protein attenuates the lytic response in glucocorticoid-treated human leukemia cells (Thulasi, R. et al, 1993). However, P1798 cells stably transfected with c-Myc expression vectors are sensitive to glucocorticoid-mediated G0 arrest. Such transformants withdraw from the cell cycle when treated with dexamethasone. P1798 cells were transformed to express both c-Myc protein and cyclin D3 in the presence of glucocorticoids. These Myc/D3 cells continue to proliferate in the presence of dexamethasone, and virtually all of these cells are capable of entering S phase in the presence of the steroid. Rapid apoptotic cell death occurs when wild-type P1798 cells are

treated with dexamethasone in serum-free medium. The myc-transformed and cyclin D3-transformed cells also die rapidly when treated with glucocorticoids in the absence of serum. T antigen transformants are resistant to glucocorticoid-mediated apoptosis in serum-free medium. Double transformants that express both cyclin D3 and c-Myc are also resistant to apoptosis in the presence of dexamethasone. The authors conclude that inhibition of both CcnD3 and c-Myc genes is crit. to glucocorticoid-mediated G0 arrest. Furthermore, those genes that convey resistance to growth arrest also convey resistance to cell death.

CC 2-4 (Mammalian Hormones)
Section cross-reference(s): 15

ST glucocorticoid gene **cmyc** CcnD3 lymphocyte proliferation; cyclin D3 gene glucocorticoid lymphocyte proliferation

IT Gene, animal
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(CcnD3; gene **c-myc** and cyclin D3 involvement in glucocorticoid inhibition of lymphoid cell proliferation)

IT Apoptosis
Cell cycle
Cell proliferation
Phosphorylation, biological
Signal transduction, biological
(gene **c-myc** and cyclin D3 involvement in glucocorticoid inhibition of lymphoid cell proliferation)

IT Gene, animal
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(RB1, gene **c-myc** and cyclin D3 involvement in glucocorticoid inhibition of lymphoid cell proliferation)

IT Lymphocyte
(T-cell, gene **c-myc** and cyclin D3 involvement in glucocorticoid inhibition of lymphoid cell proliferation)

IT Gene, animal
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**c-myc**, gene **c-myc** and cyclin D3 involvement in glucocorticoid inhibition of lymphoid cell proliferation)

IT Phosphoproteins
RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(cyclins D3, gene **c-myc** and cyclin D3 involvement in glucocorticoid inhibition of lymphoid cell proliferation)

IT Ribonucleic acid formation factors
RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(gene Rb, gene **c-myc** and cyclin D3 involvement in glucocorticoid inhibition of lymphoid cell proliferation)

IT Corticosteroids, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(gluco-, gene **c-myc** and cyclin D3 involvement in glucocorticoid inhibition of lymphoid cell proliferation)

IT 50-02-2, Dexamethasone
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(gene **c-myc** and cyclin D3 involvement in glucocorticoid inhibition of lymphoid cell proliferation)

IT 147014-97-9, **Cdk4** kinase
RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(gene **c-myc** and cyclin D3 involvement in

glucocorticoid **inhibition** of lymphoid cell proliferation)

L21 ANSWER 1 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:85166 HCAPLUS
DOCUMENT NUMBER: 136:273464
TITLE: Early gene expression changes preceding thyroid hormone-induced involution of a thyrotrope tumor
AUTHOR(S): Wood, William M.; Sarapura, Virginia D.; Dowding, Janet M.; Woodmansee, Whitney W.; Haakinson, Danielle J.; Gordon, David F.; Ridgway, E. Chester
CORPORATE SOURCE: Division of Endocrinology, Metabolism and Diabetes, Department of Medicine, University of Colorado Health Sciences Center, Denver, CO, 80262, USA
SOURCE: Endocrinology (2002), 143(2), 347-359
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Treatment with thyroid hormone (TH) results in shrinkage of a thyrotropic tumor grown in a hypothyroid host. We used microarray and Northern anal. to assess the changes in gene expression that preceded tumor involution. Of the 1,176 genes on the microarray, 7 were up-regulated, whereas 40 were decreased by TH. Many of these were neuroendocrine in nature and related to growth or apoptosis. When we examd. transcripts for cell cycle regulators only cyclin-dependent kinase 2, cyclin A and p57 were down-regulated, whereas p15 was induced by TH. Retinoblastoma protein, c-myc, and mdm2 were unchanged, but E2F1 was down-regulated. TH also decreased expression of brain-derived neurotrophic factor, its receptor trkB, and the receptor for TRH. These, in addn. to two other genes, neuronatin and PB cadherin, which were up- and down-regulated, resp., showed a more rapid response to TH than the cell cycle regulators and may represent direct targets of TH. Finally, p19ARF was dramatically induced by TH, and although this protein can stabilize p53 by sequestering mdm2, we found no increase in p53 protein up to 48 h of treatment. In summary, we have described early changes in the expression of genes that may play a role in TH-induced growth arrest of a thyrotropic tumor. These include repression of specific growth factor and receptors and cell cycle genes as well as induction of other factors assocd. with growth arrest and apoptosis.

CC 2-7 (Mammalian Hormones)

IT **Antitumor** agents
(anterior pituitary gland; early gene expression changes preceding thyroid hormone-induced involution of a thyrotrope tumor)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**c-myc**; early gene expression changes preceding thyroid hormone-induced involution of a thyrotrope tumor)

IT 99676-46-7, Neuroendocrine convertase 1 141349-86-2, Cyclin-dependent kinase 2 147014-96-8, Cdk5 kinase 147014-97-9, **Cdk4** kinase 148196-69-4, Protease-nexin 1 165245-96-5, p38 MAP kinase 241475-96-7, Epithin 303014-92-8, Cdk6 kinase 362690-38-8, Protein phosphatase 2C 366806-33-9, Casein kinase II
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(early gene expression changes preceding thyroid hormone-induced involution of a thyrotrope tumor)

REFERENCE COUNT: 98 THERE ARE 98 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 2 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:51653 HCAPLUS
DOCUMENT NUMBER: 136:97268
TITLE: In vitro cell culture models that accurately mimic patterns of gene expression in vivo and their geometrical requirements
INVENTOR(S): Dangles, Virginie; Lazar, Vladimir; Bellet, Dominique
PATENT ASSIGNEE(S): Epigene, Fr.
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002004654	A2	20020117	WO 2001-FR2230	20010710
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2811335	A1	20020111	FR 2000-8991	20000710

PRIORITY APPLN. INFO.: FR 2000-8991 A 20000710

AB Methods of inducing patterns of gene expression in cultured cells that accurately mimic those found in a defined cell type in vivo are described. Specifically, methods of mimicking gene expression in tumor cells are described. In part, the methods involve developing systems where the cultured have spatial relationships with one another that are comparable to those found in vivo such as the use of spherical culture systems to resemble three-dimensional relationships. The invention also concerns a method for identifying or confirming that a gene shows different patterns of expression in normal and abnormal cells. The invention further concerns a method for selecting a compd. capable of being used as medicine for treating and/or preventing an alteration in the expression of a gene of interest. Finally, the invention concerns the use of said detd. in vitro models, in particular three-dimensional spheroid-type models as relevant model for studying expression of at least a gene of interest. Patterns of expression of tumor marker genes were studied in cultured bladder cancer tumors. Levels of expression varied greatly between cells cultured as 2-dimensional films and in 3-dimensional spherules. The gene for the .beta. subunit of human chorionic gonadotrophin could show differences of 675-fold in levels of expression between film and spherical cultures. Spherical cultures more effectively mimicked patterns of gene expression seen in vivo.

IC ICM C12Q
CC 3-1 (Biochemical Genetics)
Section cross-reference(s): 1, 9, 14
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**CDK4**, patterns of expression of; in vitro cell culture models that accurately mimic patterns of gene expression in vivo and their geometrical requirements)
IT Gene, animal

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**c-myc**, patterns of expression of; in vitro cell culture models that accurately mimic patterns of gene expression in vivo and their geometrical requirements)

IT **Drug screening**
(for **anticancer drugs**, cell cultures for; in vitro cell culture models that accurately mimic patterns of gene expression in vivo and their geometrical requirements)

IT **Antitumor** agents
(**screening** for, cell cultures for; in vitro cell culture models that accurately mimic patterns of gene expression in vivo and their geometrical requirements)

L21 ANSWER 3 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:31681 HCAPLUS
DOCUMENT NUMBER: 136:97255
TITLE: Diagnosis and therapy of astrocytomas by detection of single nucleotide polymorphism and cytosine methylation in chemically modified genomic DNA
INVENTOR(S): Olek, Alexander; Piepenbrock, Christian; Berlin, Kurt
PATENT ASSIGNEE(S): Epigenomics Ag, Germany
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 69
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002002808	A2	20020110	WO 2001-EP7538	20010702
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 10032529	A1	20020207	DE 2000-10032529	20000630

PRIORITY APPLN. INFO.: DE 2000-10032529 A 20000630
DE 2000-10043826 A 20000901

AB The invention relates to chem. modified genomic sequences of genes assocd. with astrocytomas, an oligonucleotide directed against said sequence and/or PNA oligomers for the detection of the methylation state of cytosine of genes assocd. with astrocytomas. The present invention is based on the discovery that cytosine methylations patterns in genomic DNA are particularly suitable for diagnosis and/or therapy of astrocytomas. Thus, the chem. modified genomic sequences of genes assocd. with astrocytomas, and oligonucleotides and/or peptide nucleic acid oligomers for detecting the cytosine methylation state of astrocytoma-assocd. genes are provided. Specific reaction of bisulfite and subsequent alk. hydrolysis converts cytosine to uracil, which corresponds to thymidine in its base pairing behavior. However, 5-methylcytosine remains unmodified under these conditions. Consequently, the original DNA is converted in such a manner that methylcytosine, which originally could not be distinguished from cytosine by its hybridization behavior, can now be detected as the only remaining cytosine using "normal" mol. biol. techniques. The oligomer probes according to the present invention,

contg. at least one CpG dinucleotide, constitute important and effective tools which make it possible to ascertain the genetic and epigenetic parameters of genes assocd. with astrocytomas. The invention is exemplified by methylation anal. of the transforming growth factor-.alpha., MLH1, CSNK2B, and NF1 genes.

IC ICM C12Q001-68

CC 3-1 (Biochemical Genetics)
Section cross-reference(s): 9, 13, 14

IT Gene, animal
RL: ANT (Analyte); DGN (Diagnostic use); PRP (Properties); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**CDK4**; diagnosis and therapy of astrocytomas by detection of single nucleotide polymorphism and cytosine methylation in chem. modified genomic DNA)

IT **Antitumor** agents
Astrocyte
(astrocytoma; diagnosis and therapy of astrocytomas by detection of single nucleotide polymorphism and cytosine methylation in chem. modified genomic DNA)

IT Gene, animal
RL: ANT (Analyte); DGN (Diagnostic use); PRP (Properties); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**c-myc**; diagnosis and therapy of astrocytomas by detection of single nucleotide polymorphism and cytosine methylation in chem. modified genomic DNA)

L21 ANSWER 4 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:10522 HCAPLUS
DOCUMENT NUMBER: 136:65176
TITLE: Detection of single nucleotide polymorphism and cytosine methylation in genes associated with differentiation of astrocytoma, oligoastrocytoma, and oligodendroglioma tumor cells using chemically modified genomic DNA
INVENTOR(S): Olek, Alexander; Piepenbrock, Christian; Berlin, Kurt
PATENT ASSIGNEE(S): Epigenomics A.-G., Germany
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 69
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002000705	A2	20020103	WO 2001-EP7539	20010702
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 10032529	A1	20020207	DE 2000-10032529	20000630

PRIORITY APPLN. INFO.: DE 2000-10032529 A 20000630
DE 2000-10043826 A 20000901

AB The invention relates to chem. modified genomic sequences of genes assocd. with differentiation of astrocytoma, oligoastrocytoma, and

oligodendroglioma tumor cells, oligonucleotides directed against said sequences and/or PNA oligomers for the detection of the methylation state of cytosine of these genes. The present invention is based on the discovery that cytosine methylations patterns in genomic DNA are particularly suitable for diagnosis and/or therapy of these tumors. Thus, the chem. modified genomic sequences of the genes, and oligonucleotides and/or peptide nucleic acid oligomers for detecting the cytosine methylation state of the tumor-assocd. genes are provided. Specific reaction of bisulfite and subsequent alk. hydrolysis converts cytosine to uracil, which corresponds to thymidine in its base pairing behavior. However, 5-methylcytosine remains unmodified under these conditions. Consequently, the original DNA is converted in such a manner that methylcytosine, which originally could not be distinguished from cytosine by its hybridization behavior, can now be detected as the only remaining cytosine using "normal" mol. biol. techniques. The oligomer probes according to the present invention, contg. at least one CpG dinucleotide, constitute important and effective tools which make it possible to ascertain the genetic and epigenetic parameters of genes assocd. differentiating astrocytoma, oligoastrocytoma, and oligodendroglioma tumor cells. The invention is exemplified by methylation anal. of genes DAPK1, TNFB, and CDK4.

IC ICM C07K014-435

CC 3-1 (Biochemical Genetics)
Section cross-reference(s): 9, 14

IT Gene, animal
RL: ANT (Analyte); DGN (Diagnostic use); PRP (Properties); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**CDK4**; detection of single nucleotide polymorphism and cytosine methylation in genes assocd. with differentiation of astrocytoma, oligoastrocytoma, and oligodendroglioma tumor cells using chem. modified genomic DNA)

IT **Antitumor** agents
Astrocyte
(astrocytoma; detection of single nucleotide polymorphism and cytosine methylation in genes assocd. with differentiation of astrocytoma, oligoastrocytoma, and oligodendroglioma tumor cells using chem. modified genomic DNA)

IT Gene, animal
RL: ANT (Analyte); DGN (Diagnostic use); PRP (Properties); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**c-myc**; detection of single nucleotide polymorphism and cytosine methylation in genes assocd. with differentiation of astrocytoma, oligoastrocytoma, and oligodendroglioma tumor cells using chem. modified genomic DNA)

IT **Antitumor** agents
Oligodendrocyte
(oligodendroglioma; detection of single nucleotide polymorphism and cytosine methylation in genes assocd. with differentiation of astrocytoma, oligoastrocytoma, and oligodendroglioma tumor cells using chem. modified genomic DNA)

IT 383916-28-7 383916-29-8 384386-45-2 384386-46-3
RL: ARG (Analytical reagent use); DGN (Diagnostic use); PRP (Properties); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(PCR primer for gene **CDK4**; detection of single nucleotide polymorphism and cytosine methylation in genes assocd. with differentiation of astrocytoma, oligoastrocytoma, and oligodendroglioma tumor cells using chem. modified genomic DNA)

L21 ANSWER 5 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:598155 HCAPLUS

DOCUMENT NUMBER: 135:176488
TITLE: **Cyclin dependent kinase 4** gene as a target for transcription factor **c-MYC** and a reporter construct useful for cancer **drug screening**
INVENTOR(S): Vogelstein, Bert; Kinzler, Kenneth W.; Hermeking, Heiko
PATENT ASSIGNEE(S): Johns Hopkins University, USA
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001059090	A2	20010816	WO 2001-US4227	20010209
WO 2001059090	A3	20020307		

W: AU, CA
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR

PRIORITY APPLN. INFO.: US 2000-181930P P 20000211

AB The prototypic oncogene c-MYC encodes a transcription factor, which can drive proliferation by promoting cell cycle re-entry. However, the mechanisms through which c-MYC achieves these effects have been unclear. Using serial anal. of gene expression (SAGE), we have identified the cyclin dependent kinase 4 (CDK4) gene as a transcriptional target of c-MYC. C-MYC induced a rapid increase in CDK4 mRNA levels through four highly conserved c-MYC binding sites (MBS) within the CDK4 promoter. Cell cycle progression is delayed in c-MYC-deficient RAT1 cells, and this delay was assocd. with a defect in CDK4 induction. Ectopic expression of CDK4 in these cells partially alleviated the growth defect. Thus CDK4 provides a direct link between the oncogenic effects of c-MYC and cell cycle regulation. The invention also provides a reporter construct comprising an upstream region of mammalian CDK4 gene, which comprises at least four c-MYC binding sites, and a coding sequence for a reporter protein for cancer drug screening. The invention further provides methods and host cells comprising a reporter construct and a c-MYC protein to identify anti-tumor agents.

IC ICM C12N015-00
CC 3-4 (Biochemical Genetics)
Section cross-reference(s): 1
ST gene **cdk4** transcription factor MYC reporter construct; **antitumor** agent **screening** reporter construct; cell cycle regulation **cdk4** MYC
IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(**APC**; reporter construct useful for **screening** cancer **drugs** inhibiting growth of tumor cells which have a **mutation** in **APC**)
IT Lymphoma
(**Burkitt**'s; reporter construct useful for **screening** cancer **drugs** which inhibit tumor cell growth)
IT Transcriptional regulation
(activation; **cyclin dependent kinase 4** gene as a target for transcription factor **c-MYC** and a reporter construct useful for cancer **drug screening**)

IT Recombination, genetic
(amplification; reporter construct useful for **screening** cancer **drugs** inhibiting growth of tumor cells which have amplification of **c-MYC**)
IT Transcription factors
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**c-myc**; **cyclin dependent kinase 4** gene as a target for transcription factor **c-MYC** and a reporter construct useful for cancer **drug screening**)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**cdk4**; **cyclin dependent kinase 4** gene as a target for transcription factor **c-MYC** and a reporter construct useful for cancer **drug screening**)
IT Intestine, neoplasm
(colon; reporter construct useful for **screening** cancer **drugs** which inhibit tumor cell growth)
IT **Antitumor** agents
Drug screening
Genetic vectors
(**cyclin dependent kinase 4** gene as a target for transcription factor **c-MYC** and a reporter construct useful for cancer **drug screening**
)
IT Reporter gene
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**cyclin dependent kinase 4** gene as a target for transcription factor **c-MYC** and a reporter construct useful for cancer **drug screening**
)
IT **Mutation**
(deletion; reporter construct useful for **screening** cancer **drugs** inhibiting growth of tumor cells which have a **mutation** in **APC**)
IT Genetic element
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(gene **c-myc** phosphoprotein-responsive element; reporter construct useful for cancer **drug screening** comprising the upstream region of **cdk4** gene)
IT Nerve, neoplasm
(**neuroblastoma**; reporter construct useful for **screening** cancer **drugs** which inhibit tumor cell growth)
IT Cyclin dependent kinase inhibitors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(p16INK4; **cyclin dependent kinase 4** gene as a target for transcription factor **c-MYC** and a reporter construct useful for cancer **drug screening**)
IT Promoter (genetic element)
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(reporter construct useful for cancer **drug screening** comprising the upstream region of **cdk4** gene)

IT Proliferation inhibition
(reporter construct useful for **screening** cancer **drugs** which inhibit tumor cell growth)
IT Recombination, genetic
(**translocation**, t8;14; reporter construct useful for **screening** cancer **drugs** inhibiting growth of tumor cells which have a **translocation**)
IT **Catenins**
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(.beta.-; reporter construct useful for **screening** cancer **drugs** inhibiting growth of tumor cells which have a **mutation** in .beta.-**catenin**)
IT 86691-56-7
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**c-MYC** binding site; **cyclin dependent kinase 4** gene as a target for transcription factor **c-MYC** and a reporter construct useful for cancer **drug screening**)
IT 354848-99-0 354849-00-6 354849-01-7 354849-02-8 354849-03-9 354849-04-0, 6: PN: WO0159090 SEQID: 6 unclaimed DNA 354849-05-1, 7: PN: WO0159090 SEQID: 7 unclaimed DNA 354849-06-2, 8: PN: WO0159090 SEQID: 8 unclaimed DNA 354849-07-3, 9: PN: WO0159090 SEQID: 9 unclaimed DNA 354849-08-4 354849-09-5 354849-11-9, 12: PN: WO0159090 FIG: B unclaimed DNA
RL: PRP (Properties)
(unclaimed nucleotide sequence; **cyclin dependent kinase 4** gene as a target for transcription factor **c-MYC** and a reporter construct useful for cancer **drug screening**)
IT 354849-10-8
RL: PRP (Properties)
(unclaimed sequence; **cyclin dependent kinase 4** gene as a target for transcription factor **c-MYC** and a reporter construct useful for cancer **drug screening**)

L21 ANSWER 6 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:506424 HCAPLUS
DOCUMENT NUMBER: 135:240015
TITLE: Distinctive gene expression profiles associated with Hepatitis B virus .times. protein
AUTHOR(S): Wu, Chuan-Ging; Salvay, David M.; Forgues, Marshonna; Valerie, Kristoffer; Farnsworth, Julie; Markin, Rodney S.; Wang, Xin Wei
CORPORATE SOURCE: Laboratory of Human Carcinogenesis, National Cancer Institute, Bethesda, MD, 20892-4255, USA
SOURCE: Oncogene (2001), 20(28), 3674-3682
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Hepatitis B virus (HBV) is a major risk factor for the development of hepatocellular carcinoma (HCC). HBV encodes the potentially oncogenic HBx protein, which mainly functions as a transcriptional co-activator involving in multiple gene deregulations. However, mechanisms underlying HBx-mediated oncogenicity remain unclear. To det. the role(s) of HBx in the early genesis of HCC, we utilized the NCI Oncochip microarray that contains 2208 human cDNA clones to examine the gene expression profiles in

either freshly isolated normal primary adult human hepatocytes (Hhep) or an HCC cell line (SK-Hep-1) ecotopically expressing HBx via an adenoviral system. The gene expression profiles also were detd. in liver samples from HBV-infected chronic active hepatitis patients when compared with normal liver samples. The microa The microarray results were validated through Northern blot anal. of the expression of selected genes. Using reciprocally labeling hybridizations, scatter-plot anal. of gene expression ratios in human primary hepatocytes expressing HBx demonstrates that microarrays are highly reproducible. The comparison of gene expression profiles between HBx-expressing primary hepatocytes and HBV-infected liver samples shows a consistent alteration of many cellular genes including a subset of oncogenes (such as c-myc and c-myb) and tumor suppressor genes (such as APC, p53, WAF1 and WT1). Furthermore, clustering algorithm anal. showed distinctive gene expression profiles in Hhep and SK-Hep-1 cells. Our findings are consistent with the hypothesis that the deregulation of cellular genes by oncogenic HBx may be an early event that favors hepatocyte proliferation during liver carcinogenesis.

CC 14-1 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 3

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**Cdk4**; distinctive human gene expression profiles assocd. with hepatitis B virus .times. protein in relation to liver carcinogenesis)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(adenine nucleotide **translocator** 2-encoding; distinctive human gene expression profiles assocd. with hepatitis B virus .times. protein in relation to liver carcinogenesis)

IT Proteins, specific or class
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(adenine nucleotide **translocator** 2; distinctive human gene expression profiles assocd. with hepatitis B virus .times. protein in relation to liver carcinogenesis)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**c-myc**; distinctive human gene expression profiles assocd. with hepatitis B virus .times. protein in relation to liver carcinogenesis)

IT Proteins, specific or class
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene **c-myc**; distinctive human gene expression profiles assocd. with hepatitis B virus .times. protein in relation to liver carcinogenesis)

IT 9001-12-1, Matrix metalloproteinase-1 9026-43-1, Protein kinase 9031-61-2, Thymidylate synthase 9036-23-1, UMP kinase 9054-63-1, Aminopeptidase N 50812-37-8, Glutathione S-transferase 67763-96-6, IGF-1 79747-53-8, Tyrosine phosphatase 146702-84-3, MEK kinase 1 147014-97-9, **Cyclin-dependent kinase 4** 182762-08-9, caspase-4 192230-91-4, MAP kinase kinase 3 360563-69-5, Gene A6 protein kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(distinctive human gene expression profiles assocd. with hepatitis B virus .times. protein in relation to liver carcinogenesis)

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 7 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:489619 HCAPLUS
DOCUMENT NUMBER: 135:71268
TITLE: Use of locked nucleic acid-modified oligonucleotides for treatment of cancer and inflammation
INVENTOR(S): Orum, Henrik; Koch, Troel; Skouv, Jan; Jakobsen, Mogen Havsteen
PATENT ASSIGNEE(S): Exiqon A/S, Den.
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001048190	A2	20010705	WO 2000-IB2043	20001222

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-171873P P 19991223

AB The invention relates to therapeutic applications of LNA-modified oligonucleotides. In particular, the invention provides methods for treatment of undesired cell growth as well as treatment of inflammatory related diseases and disorders. Preferably, administration of an LNA-modified oligonucleotide modulates expression of a targeted gene assocd. with the undesired cell growth or an inflammatory related disease or disorder. Thus, the peritoneal cells of rats injected i.p. with LNA-contg. oligonucleotides directed to Fc.epsilon.R1.alpha. mRNA produced less Fc.epsilon.R1.alpha. and released less histamine than did rats given unmodified oligonucleotides.

IC ICM C12N015-11
ICS A61K031-712; C07H021-00; A61P029-00; A61P035-00
CC 1-6 (Pharmacology)
Section cross-reference(s): 3
ST locked nucleic acid oligonucleotide **antitumor** antiinflammatory
IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**CDK4**, inhibition of expression of; use of locked nucleic acid-modified oligonucleotides for treatment of cancer and inflammation)
IT **Antitumor** agents
(brain; use of locked nucleic acid-modified oligonucleotides for treatment of cancer and inflammation)
IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**c-myc**, inhibition of expression of; use of locked nucleic acid-modified oligonucleotides for treatment of cancer and inflammation)

IT **Antitumor** agents
(colon; use of locked nucleic acid-modified oligonucleotides for treatment of cancer and inflammation)
IT **Antitumor** agents
(hepatoma; use of locked nucleic acid-modified oligonucleotides for treatment of cancer and inflammation)
IT **Antitumor** agents
(leukemia; use of locked nucleic acid-modified oligonucleotides for treatment of cancer and inflammation)
IT **Antitumor** agents
(lung; use of locked nucleic acid-modified oligonucleotides for treatment of cancer and inflammation)
IT **Antitumor** agents
(ovary; use of locked nucleic acid-modified oligonucleotides for treatment of cancer and inflammation)
IT **Antitumor** agents
(prostate gland; use of locked nucleic acid-modified oligonucleotides for treatment of cancer and inflammation)
IT **Antitumor** agents
(small intestine; use of locked nucleic acid-modified oligonucleotides for treatment of cancer and inflammation)
IT **Antitumor** agents
(stomach; use of locked nucleic acid-modified oligonucleotides for treatment of cancer and inflammation)
IT **Antitumor** agents
(testis; use of locked nucleic acid-modified oligonucleotides for treatment of cancer and inflammation)
IT Anti-inflammatory agents
Antitumor agents
(use of locked nucleic acid-modified oligonucleotides for treatment of cancer and inflammation)

L21 ANSWER 8 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:338762 HCAPLUS
DOCUMENT NUMBER: 134:362292
TITLE: Methods of determining individual hypersensitivity to a pharmaceutical agent from gene expression profile
INVENTOR(S): Farr, Spencer
PATENT ASSIGNEE(S): Phase-1 Molecular Toxicology, USA
SOURCE: PCT Int. Appl., 222 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032928	A2	20010510	WO 2000-US30474	20001103

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-165398P P 19991105
US 2000-196571P P 20000411

AB The invention discloses methods, gene databases, gene arrays, protein arrays, and devices that may be used to det. the hypersensitivity of individuals to a given agent, such as drug or other chem., in order to prevent toxic side effects. In one embodiment, methods of identifying hypersensitivity in a subject by obtaining a gene expression profile of multiple genes assocd. with hypersensitivity of the subject suspected to be hypersensitive, and identifying in the gene expression profile of the subject a pattern of gene expression of the genes assocd. with hypersensitivity are disclosed. The gene expression profile of the subject may be compared with the gene expression profile of a normal individual and a hypersensitive individual. The gene expression profile of the subject that is obtained may comprise a profile of levels of mRNA or cDNA. The gene expression profile may be obtained by using an array of nucleic acid probes for the plurality of genes assocd. with hypersensitivity. The expression of the genes predetd. to be assocd. with hypersensitivity is directly related to prevention or repair of toxic damage at the tissue, organ or system level. Gene databases arrays and app. useful for identifying hypersensitivity in a subject are also disclosed.

IC ICM C12Q001-68
ICS G01N033-50

CC 3-4 (Biochemical Genetics)
Section cross-reference(s): 1, 6, 7, 13, 15

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(adenine nucleotide **translocator** 1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**c-myc** binding protein; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**c-myc**; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**cdk4**; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 107-97-1, Sarcosin 447-41-6, Nylidrin 8056-51-7 9000-86-6, Alanine aminotransferase 9000-97-9 9001-05-2, Catalase 9001-40-5, Glucose-6-phosphate dehydrogenase 9001-48-3, Glutathione reductase 9001-50-7, Glyceraldehyde 3-phosphate dehydrogenase 9001-62-1, Hepatic lipase 9001-84-7, Phospholipase A2 9002-03-3, Dihydrofolate reductase 9002-06-6, Thymidine kinase 9002-12-4, Urate oxidase 9002-67-9, Luteinizing hormone 9003-99-0, Myeloperoxidase 9012-25-3, Catechol-O-methyltransferase 9012-38-8, PAPS synthetase 9012-39-9 9012-52-6, S-Adenosylmethionine synthetase 9013-08-5, Phosphoenolpyruvate carboxykinase 9013-18-7, Fatty acyl-CoA synthetase 9013-38-1, Dopamine .beta.-hydroxylase 9013-66-5, Glutathione peroxidase 9013-79-0, Neuropathy target esterase 9014-55-5, Tyrosine aminotransferase 9015-71-8, Corticotropin releasing hormone 9015-81-0, 17-.beta. Hydroxysteroid dehydrogenase 9016-12-0, Hypoxanthine-guanine

phosphoribosyltransferase 9023-44-3, Tryptophanyl-tRNA synthetase 9023-62-5, Glutathione synthetase 9023-64-7, .gamma.-Glutamylcysteinyl synthetase 9023-70-5, Glutamine synthetase 9024-60-6, Ornithine decarboxylase 9024-61-7, Histidine decarboxylase 9025-32-5, Prolidase 9026-00-0, Cholesterol esterase 9026-09-9, Phenol sulfotransferase 9026-43-1, Serine kinase 9026-51-1, Nucleoside diphosphate kinase 9027-13-8, Enoyl-CoA hydratase 9027-65-0, Acyl-CoA dehydrogenase 9028-06-2 9028-31-3, Aldose reductase 9028-35-7, HMG CoA reductase 9028-41-5, Hydroxyacyl-Coenzyme A dehydrogenase 9028-86-8, Aldehyde dehydrogenase 9029-73-6, Phenyl alanine hydroxylase 9029-80-5, Histamine N-methyltransferase 9029-97-4, 3-Ketoacyl-CoA thiolase 9031-37-2, Ceruloplasmin 9031-54-3, Sphingomyelinase 9031-61-2, Thymidylate synthase 9031-72-5, Alcohol dehydrogenase 9032-20-6, DT-Diaphorase 9035-58-9, Blood-coagulation factor III 9036-22-0, Tyrosine hydroxylase 9037-21-2, Tryptophan hydroxylase 9037-62-1, Glycyl tRNA synthetase 9039-06-9, NADPH cytochrome P450 reductase 9040-57-7, Ribonucleotide reductase 9041-92-3 9045-77-6, Fatty acid synthase 9046-27-9, .gamma.-Glutamyl transpeptidase 9048-63-9, Epoxide hydrolase 9055-67-8, Poly(ADP-ribose)polymerase 9059-25-0, Lysyl oxidase 9068-41-1, Carnitine palmitoyltransferase 9074-02-6, Malic enzyme 9074-10-6, Biliverdin reductase 9074-19-5, Hydratase 9074-87-7, .gamma.-Glutamyl hydrolase 9081-36-1, 25-Hydroxyvitamin D3 1-hydroxylase 11096-26-7, Erythropoietin 37205-63-3, ATP synthase 37237-44-8, Glucosylceramide synthase 37289-06-8, Acid ceramidase 37292-81-2, Cytochrome p 450 11A1 37318-49-3, Protein disulfide isomerase 39391-18-9, Prostaglandin H synthase 52228-01-0 56093-23-3, .alpha.-1,2-Fucosyl transferase 56645-49-9, Cathepsin G 59536-73-1, Phosphomannomutase 59536-74-2, Very long-chain acyl-CoA dehydrogenase 60267-61-0, Ubiquitin 60616-82-2, Cathepsin L 61116-22-1, Fatty acyl-CoA oxidase 62229-50-9, Epidermal growth factor 67339-09-7, Thiopurine methyltransferase 67763-96-6, Insulin-like growth factor 1 67763-97-7, Insulin-like growth factor II 77271-19-3, 6-O-Methylguanine-DNA methyltransferase 77847-96-2, Prostacyclin-stimulating factor 79747-53-8, Protein tyrosine phosphatase 79955-99-0, Stromelysin-1 80146-85-6, Tissue Transglutaminase 80295-41-6, Complement component C3 81627-83-0, Colony stimulating factor -1 82391-43-3, 12-Lipoxygenase 83268-44-4 83869-56-1, Granulocyte-macrophage colony-stimulating factor 85637-73-6, Atrial natriuretic factor 87397-91-9, Thymosin .beta.10 88943-21-9, Proteinase .alpha.1-inhibitor III 89964-14-7, Prothymosin, alpha 90698-26-3, Ribosomal protein S6 kinase 92767-51-6, O-6-Alkylguanine-DNA-alkyltransferase 96024-44-1, Granulin 105238-46-8, Macropain 106096-92-8, Fibroblast growth factor, acidic 106956-32-5, Oncostatin M 112130-98-0, Procathepsin L 114949-22-3, Activin (protein) 117698-12-1, Paraoxonase 119418-04-1, Galanin 123626-67-5, Endothelin-1 125978-95-2, Nitric oxide synthase 127464-60-2, Vascular endothelial growth factor 137632-07-6, Extracellular-signal-regulated kinase 1 138238-81-0, Endothelin converting enzyme-1 140208-24-8, Tissue inhibitor of metalloproteinase-1 141176-92-3 141349-86-2, Cyclin dependent kinase 2 141436-78-4, Protein kinase C 142243-03-6, Plasminogen activator inhibitor 2 142805-56-9, DNA topoisomerase II 142805-58-1, MAP kinase kinase 143180-75-0, DNA topoisomerase I 143375-65-9, Cyclin dependent kinase 1 145809-21-8, Tissue inhibitor of metalloproteinase-3 146480-35-5, Matrix metalloproteinase-2 147014-97-9, **Cyclin dependent kinase 4** 148348-15-6, Fibroblast growth factor 7 149316-81-4, Branched chain acyl-CoA oxidase 149371-05-1, Kinase (phosphorylating), gene c-abl protein 149885-78-9, Hepatocyte growth factor activator 154907-65-0, Checkpoint kinase 155807-64-0, FEN-1 Endonuclease 165245-96-5, p38 Mitogen-activated protein kinase 169592-56-7, CPP32

proteinase 179241-70-4, Protein kinase ZPK 179241-78-2, Caspase 8 182372-14-1, Caspase 2 182372-15-2, Caspase 6 182762-08-9, Caspase 4 187414-12-6, Caspase-1 189258-14-8, Caspase 7 192465-11-5, Caspase 5 193363-12-1, Vascular endothelial growth factor D 194554-71-7, Tissue factor pathway inhibitor 205944-50-9, Osteoprotegerin 220983-94-8, Sorbitol dehydrogenase 289898-51-7, JNK1 protein kinase 303752-61-6, DNA dependent protein kinase 329736-03-0, Cytochrome p450 3A4 329764-85-4, Cytochrome p450 1A1 329900-75-6, Cyclooxygenase 2 329978-01-0, Cytochrome p450 2C9 330196-64-0, Cytochrome p450 1A2 330196-93-5, Cytochrome p450 2E1 330207-10-8, Cytochrome p450 2B1 330589-90-7, Cytochrome p450 2C19 330596-22-0, Cytochrome p450 1B1 330597-62-1, Cytochrome p450 2D6 330975-22-9, Macrostatin 331462-97-6, Cytochrome p450 2B2 331462-98-7, Cytochrome p450 3A1 331823-00-8, Cytochrome p450 2C11 331823-12-2, Cytochrome p450 2C12 331823-27-9, Cytochrome p450 2A1 331827-06-6, Cytochrome p450 2A6 332847-52-6, Cytochrome p450 4A 336884-26-5, Cytochrome p450 2B10 338964-08-2, P 450 17A 338969-62-3, P 450 2A3 338969-69-0, P 450 2F2 338969-71-4, P 450 4A1
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

L21 ANSWER 9 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:265645 HCAPLUS
DOCUMENT NUMBER: 134:292402
TITLE: Methods for identifying RNA binding compounds
INVENTOR(S): Rana, Tariq M.
PATENT ASSIGNEE(S): University of Medicine and Dentistry of New Jersey, USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001025486	A1	20010412	WO 2000-US27389	20001004

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-157646P P 19991004
AB The present invention relates to methods of screening for compds. that bind RNA mols. In particular, the methods of the invention comprise screening a library of test compds., each of which is attached to a solid support, with a dye-labeled RNA mol. to form a dye-labeled target RNA: support-attached test compd. complex. By virtue of the dye label on the target RNA, the support becomes labeled and can be sepd. from unlabeled solid supports. The present invention further relates to methods of inhibiting an RNA-protein interaction, to methods of screening for compds. that increase or decrease the prodn. of a protein, and to methods of screening for a compd. that is capable of treating or preventing a disease

whose progression is assocd. with an in vivo binding of a test compd. to a target RNA.
IC ICM C12Q001-68
ICS C07H019-00; C07H021-00; A61K038-00
CC 9-16 (Biochemical Methods)
Section cross-reference(s): 1
IT Proteins, specific or class
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**c-myc**; methods for identifying RNA binding compds.)
IT AIDS (disease)
Buffers
Candida
Composition
Cotton
Detergents
Diarrhea
Disease, animal
Disperse dyes
Drug screening
Dyes
Electrospray ionization mass spectrometry
Encephalitis
Fluorescent dyes
HPLC
Influenza
Legionella
Leukotriene antagonists
Libraries
Malaria
Meningitis
Molecules
NMR spectroscopy
Pertussis
Pneumonia
Protein sequence analysis
Rotavirus
Separation
Sepsis
Solutions
Surfactants
Syphilis
Tinea (skin disease)
X-ray photoelectron spectroscopy
(methods for identifying RNA binding compds.)
IT 147014-97-9, Cyclin-dependent kinase **cdk4**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor; methods for identifying RNA binding compds.)
IT 9000-83-3
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(proton-**translocating**; calcium-activated,)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 10 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:247464 HCAPLUS
DOCUMENT NUMBER: 134:277614
TITLE: Recognition of differences in cell cycle structure between stem and differentiated cells
INVENTOR(S): Rathjen, Peter David; Dalton, Stephen

PATENT ASSIGNEE(S): Luminis Pty. Ltd., Australia
SOURCE: PCT Int. Appl., 105 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001023531	A1	20010405	WO 2000-AU1184	20000922

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: AU 1999-3073 A 19990924

AB The invention resides in the recognition of differences in cell cycle structure between stem and differentiated cells. Pluripotent cells spend .apprx.65% of their time is S phase, .apprx.15% in G1 and .apprx.20% in M. Partially differentiated cells have a different cell cycle structure, e.g. mesoderm spend 15-20% of time in S phase, and 60% in G1. These differences in cell cycle have lead to the identification of differences in expression of cell cycle genes and activity of regulators. The claims are directed to manipulating cell cycles genes, regulators and proteins to regulate cell activity or cells cycle, identify cell types, facilitate maintenance, reprogram cells, or regulate differentiation in pluripotent or multipotent cells. The methods include manipulating the expression and/or activity of a cell cycle regulatory mol. selected from a cyclin, a cyclin-dependent protein kinase, a Cdk inhibitor, upstream regulators or biochem. targets thereof, and/or a tumor suppressor protein.

IC ICM C12N005-08
ICS C12N005-06

CC 9-11 (Biochemical Methods)
Section cross-reference(s): 3, 13

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(**c-myc**; recognition of differences in cell cycle structure between stem and differentiated cells)

IT **Antitumor** agents
Cell cycle
Cell differentiation
Cell proliferation
Cyclin dependent kinase inhibitors
Drug delivery systems
Gene therapy
Genetic engineering
Nuclear transplantation
Regeneration, animal
(recognition of differences in cell cycle structure between stem and differentiated cells)

IT 141349-86-2, CDK2 kinase 142243-02-5, MAP kinase 146279-89-2, Cyclin E/cdk2 kinase 147014-97-9, **CDK4** kinase 150428-23-2, Cyclin-dependent protein kinase 303014-92-8, CDK6 kinase

RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(recognition of differences in cell cycle structure between stem and differentiated cells)

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 11 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:292689 HCAPLUS
DOCUMENT NUMBER: 133:187715
TITLE: **Antitumor** protein (AP) from a mushroom induced apoptosis to transformed human keratinocyte by controlling the status of pRB, **c-myc**, cyclin E-cdk2, and p21 WAF1 in the G1/S transition
AUTHOR(S): Kawamura, Yukio; Manabe, Mariko; Kitta, Kazumi
CORPORATE SOURCE: National Food Research Institute, Tsukuba, 305-8642, Japan
SOURCE: Animal Cell Technology: Challenges for the 21st Century, Proceedings of the Joint International Meeting of the Japanese Association for Animal Cell Technology (JAACT) and the European Society for Animal Cell Technology (ESACT), 2nd, Kyoto, July 26-30, 1998 (1999), Meeting Date 1998, 265-271. Editor(s): Ikura, Kouji. Kluwer Academic Publishers: Dordrecht, Neth. CODEN: 68WIAS
DOCUMENT TYPE: Conference
LANGUAGE: English

AB Antitumor protein (AP) from a mushroom, induced the morphol. changes typical to apoptosis such as nuclear condensation, aneuploidity, and DNA fragmentation at concns. as low as 5-20 ng/mL to cancer cells. Mol. alterations related to cell cycle, esp. G1/S transition were investigated with a human keratinocyte transformed with oncoproteins, E6 and E7 of human pappiloma virus(HPV)-16. AP didn't alter significantly an oncosuppressor p53 level, but induced hyperphosphorylation of pRb. Time-dependent change of G1 cyclins, cdk2 and cdk4 after addn. of AP showed that expression level of cdk inhibitors, INK4 family, and p27KIP1 did not alter, while that of p21WAF1 was downregulated.

CC 1-6 (Pharmacology)

ST **antitumor** protein apoptosis keratinocyte transcription factor

IT Interphase (cell cycle)
(G1/S boundary; **antitumor** protein (AP) from a mushroom induced apoptosis to transformed human keratinocyte by controlling status of pRB, **c-myc**, cyclin E-cdk2, and p21 WAF1 in G1/S transition)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Rb; **antitumor** protein (AP) from a mushroom induced apoptosis to transformed human keratinocyte by controlling status of pRB, **c-myc**, cyclin E-cdk2, and p21 WAF1 in G1/S transition)

IT Apoptosis
(**antitumor** protein (AP) from a mushroom induced apoptosis to transformed human keratinocyte by controlling status of pRB, **c-myc**, cyclin E-cdk2, and p21 WAF1 in G1/S transition)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**c-myc**; **antitumor** protein (AP) from a

mushroom induced apoptosis to transformed human keratinocyte by controlling status of pRB, **c-myc**, cyclin E-cdk2, and p21 WAF1 in G1/S transition)

IT Skin
(keratinocyte; **antitumor** protein (AP) from a mushroom induced apoptosis to transformed human keratinocyte by controlling status of pRB, **c-myc**, cyclin E-cdk2, and p21 WAF1 in G1/S transition)

IT Proteins, general, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mushroom; **antitumor** protein (AP) from a mushroom induced apoptosis to transformed human keratinocyte by controlling status of pRB, **c-myc**, cyclin E-cdk2, and p21 WAF1 in G1/S transition)

IT Cyclin dependent kinase inhibitors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(p21CIP1/WAF1; **antitumor** protein (AP) from a mushroom induced apoptosis to transformed human keratinocyte by controlling status of pRB, **c-myc**, cyclin E-cdk2, and p21 WAF1 in G1/S transition)

IT **Antitumor** agents
(protein; **antitumor** protein (AP) from a mushroom induced apoptosis to transformed human keratinocyte by controlling status of pRB, **c-myc**, cyclin E-cdk2, and p21 WAF1 in G1/S transition)

IT 141349-86-2 147014-97-9, **Cdk4** kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**antitumor** protein (AP) from a mushroom induced apoptosis to transformed human keratinocyte by controlling status of pRB, **c-myc**, cyclin E-cdk2, and p21 WAF1 in G1/S transition)

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 12 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:240985 HCAPLUS
DOCUMENT NUMBER: 132:292701
TITLE: Novel methods for therapeutic vaccination
INVENTOR(S): Steinaa, Lucilla; Mouritsen, Soren; Nielsen, Klaus Gregorious; Haaning, Jesper; Leach, Dana; Dalum, Iben; Gautam, Anand; Birk, Peter; Karlsson, Gunilla
PATENT ASSIGNEE(S): M Amp E Biotech A/s, Den.
SOURCE: PCT Int. Appl., 220 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000020027	A2	20000413	WO 1999-DK525	19991005
WO 2000020027	A3	20001012		

W: AE, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO,

RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9958510	A1	20000426	AU 1999-58510	19991005
EP 1117421	A2	20010725	EP 1999-945967	19991005
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, MC, IE, SI, LT, LV, FI, RO				
NO 2001001586	A	20010531	NO 2001-1586	20010328

PRIORITY APPLN. INFO.:

DK 1998-1261	A	19981005
US 1998-105011P	P	19981020
WO 1999-DK525	W	19991005

AB A method is disclosed for inducing cell-mediated immunity against cellular antigens. More specifically, the invention provides for a method for inducing cytotoxic T-lymphocyte immunity against weak antigens, notably self-proteins. The method entails that antigen presenting cells are induced to present at least one CTL epitope of the weak antigen and at the same time presenting at least one foreign T-helper lymphocyte epitope. In a preferred embodiment, the antigen is a cancer specific antigen, e.g. prostate specific membrane antigen (PSM), Her2, or FGF8b. The method can be exercised by using traditional polypeptide vaccination, but also by using live attenuated vaccines or nucleic acid vaccination. The invention furthermore provides immunogenic analogs of PSM, Her2 and FGF8b, as well as nucleic acid mols. encoding these analogs. Also vectors and transformed cells are disclosed. The invention also provides for a method for identification of immunogenic analogs of weak or non-immunogenic antigens.

IC A61K039-00

CC 15-2 (Immunochemistry)
Section cross-reference(s): 3, 63

IT Transcription factors
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**c-myc**; weak antigens inserted with foreign T cell epitope as vaccines)

IT Animal
Animal cell line
Antigen-presenting cell
Antitumor agents
Bacteriophage
Carriers
Cosmids
DNA sequences
Dendritic cell
Encapsulation
Epitopes
Immunotherapy
Influenza virus
Latex
Liposomes
Macrophage
Micelles
Molecular cloning
Mycobacterium
Particles
Plasmids
Plasmodium falciparum
Protein sequences
Quillaja saponaria

Vaccines
Virus
Virus vectors
(weak antigens inserted with foreign T cell epitope as vaccines)

IT 71965-46-3, Cathepsins 99085-47-9, Complement decay-accelerating factor 147014-97-9, **Cyclin-dependent kinase 4** 179241-78-2, Caspase 8
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(weak antigens inserted with foreign T cell epitope as vaccines)

L21 ANSWER 13 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:160183 HCAPLUS
DOCUMENT NUMBER: 133:1261
TITLE: Detection of gene amplification by genomic hybridization to cDNA microarrays
AUTHOR(S): Heiskanen, Mervi A.; Bittner, Michael L.; Chen, Yidong; Khan, Javed; Adler, Karl E.; Trent, Jeffrey M.; Meltzer, Paul S.
CORPORATE SOURCE: Cancer Genetics Branch, National Human Genome Research Institute, NIH, Bethesda, MD, 20892, USA
SOURCE: Cancer Research (2000), 60(4), 799-802
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: AACR Subscription Office
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Gene amplification is one of the major mechanisms of oncogene activation in tumorigenesis. To facilitate the identification of genes mapping to amplified regions, we have used a technique based on the hybridization of total genomic DNA to cDNA microarrays. To aid detection of the weak signals generated in this complex hybridization, we have used a tyramide-based technique that allows amplification of a fluorescent signal up to 1000-fold. Diln. expt. suggests that amplifications of 5-fold and higher can be detected by this approach. The technique was validated using cancer cell lines with several known gene amplifications, such as those affecting MYC, MYCN, ERBB2, and CDK4. In addn. to the detection of the known amplifications, we identified a novel amplified gene, ZNF133, in the neuroblastoma cell line NGP. Hybridization of NGP cDNA on an identical array also revealed over expression of ZNF133. Parallel anal. of genomic DNA for copy no. and cDNA for expression now provides rapid approach to the identification of amplified genes and chromosomal regions in tumor cells.

CC 3-1 (Biochemical Genetics)
Section cross-reference(s): 9, 14

IT Gene, animal
RL: ADV (Adverse effect, including toxicity); ANT (Analyte); ANST (Analytical study); BIOL (Biological study)
(**CDK4**; detection of gene amplification in cancer cell lines by genomic hybridization to cDNA microarrays)

IT Animal cell line
(NGP, **neuroblastoma** cell line; detection of a novel amplified gene (ZNF133) in the **neuroblastoma** cell line NGP by genomic hybridization to cDNA microarrays)

IT Gene, animal
RL: ADV (Adverse effect, including toxicity); ANT (Analyte); ANST (Analytical study); BIOL (Biological study)
(ZNF133; detection of a novel amplified gene (ZNF133) in the **neuroblastoma** cell line NGP by genomic hybridization to cDNA microarrays)

IT Gene, animal

RL: ADV (Adverse effect, including toxicity); ANT (Analyte); ANST (Analytical study); BIOL (Biological study)
(**c-myc**; detection of gene amplification in cancer cell lines by genomic hybridization to cDNA microarrays)
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 14 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:776854 HCAPLUS
DOCUMENT NUMBER: 132:106202
TITLE: Antiproliferative function of p27kip1 is frequently inhibited in highly malignant **Burkitt**'s lymphoma cells
AUTHOR(S): Barnouin, Karin; Fredersdorf, Steffen; Eddaoudi, Ayad; Mittnacht, Sibylle; Pan, Lang Xing; Du, Ming Qin; Lu, Xin
CORPORATE SOURCE: Ludwig Institute for Cancer Research, Imperial College School of Medicine at St. Mary's, London, W2 1PG, UK
SOURCE: Oncogene (1999), 18(46), 6388-6397
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Lack of detectable expression of p27kip1 cyclin dependent kinase inhibitor has previously been correlated with high degree of malignancy in human breast, colorectal, gastric and small cell lung carcinomas. Here we demonstrate that an inverse correlation between p27kip1 expression and tumor malignancy also exists in most types of human B cell lymphomas examd. A clear exception was Burkitt's lymphoma (BL), a highly malignant tumor which often expresses high levels of p27kip1. Anal. of p27kip1 derived from Burkitt's lymphoma cell lines expressing high levels of p27kip1, BL40 and BL41, in a cyclin E/cdk2 kinase inhibition assay demonstrated that p27kip1 is not permanently inactivated since heat treatment can restore the inhibitory activity of p27kip1. However, p27kip1 expressed in these two cell lines is largely sequestered in inactive complexes and we have no evidence that c-myc or Epstein-Barr virus are responsible for the sequestration of p27kip1 in these two cell lines although c-myc and EBV are two oncogenic agents often assocd. with Burkitt's lymphomas. Interestingly, we obsd. that high level p27kip1 expression often correlated with cyclin D3 overexpression both in vivo and in BL cell lines. The majority of p27kip1 in BL40 cells was complexed with cyclin D3 indicating that overexpressed cyclin D3 may at least be part of the sequestering activity for the inhibitory function of p27kip1. Furthermore, cyclinD3/cdk4 complex could sequester p27kip1 in a cyclin E/cdk2 kinase assay in vitro. Finally, we show that cyclin D3 transfected into an inducible p27kip1 cell line could overcome the G1 arrest mediated by p27kip1. These results argue that in addn. to down-regulation of p27kip1 expression, some tumor cells can sequester and tolerate the antiproliferative function of p27kip1. They also suggest a novel role for the overexpression of D-type cyclins as one pathway allowing tumor cells to overcome the antiproliferative function of p27kip1.
CC 14-1 (Mammalian Pathological Biochemistry)
ST antiproliferative function p27kip1 malignant **Burkitt** lymphoma
IT Lymphoma
(B-cell; antiproliferative function of p27kip1 is frequently inhibited in highly malignant **Burkitt**'s lymphoma cells)
IT Lymphoma
(**Burkitt**'s; antiproliferative function of p27kip1 is frequently inhibited in highly malignant **Burkitt**'s lymphoma cells)

IT Cyclins
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(D3; high expression levels of p27kip1 and cyclin D3 are assocd. in highly malignant **Burkitt**'s lymphoma cells)
IT Transformation, neoplastic
(antiproliferative function of p27kip1 is frequently inhibited in highly malignant **Burkitt**'s lymphoma cells)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**c-myc**; p27kip1 levels is independent of the expression of **c-myc** and Epstein-Barr virus in **Burkitt**'s lymphoma cells)
IT Human herpesvirus 4
(p27kip1 levels is independent of the expression of **c-myc** and Epstein-Barr virus in **Burkitt**'s lymphoma cells)
IT Cyclin dependent kinase inhibitors
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(p27KIP1; antiproliferative function of p27kip1 is frequently inhibited in highly malignant **Burkitt**'s lymphoma cells)
IT 147014-97-9, **Cdk4** kinase
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(high expression levels of p27kip1 and cyclin D3 are assocd. in highly malignant **Burkitt**'s lymphoma cells)
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 15 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:426856 HCAPLUS
DOCUMENT NUMBER: 131:54747
TITLE: Transgenic mice having modified cell-cycle regulation INK4 genes and increased susceptibility to tumor formation
INVENTOR(S): Beach, David H.; Serrano, Manuel; DePinho, Ronald A.
PATENT ASSIGNEE(S): Cold Spring Harbor Laboratory, USA; Albert Einstein College of Medicine of Yeshiva University
SOURCE: U.S., 35 pp., Cont.-in-part of U.S. Ser. No. 581,918.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 10
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5919997	A	19990706	US 1996-627610	19960404
US 5889169	A	19990330	US 1994-248812	19940525
US 5962316	A	19991005	US 1994-306511	19940914
US 6211334	B1	20010403	US 1994-346147	19941129
US 6331390	B1	20011218	US 1995-497214	19950630
US 6043030	A	20000328	US 1996-581918	19960102

PRIORITY APPLN. INFO.:
US 1993-154915 A2 19931118
US 1994-227371 A2 19940414
US 1994-248812 A2 19940525
US 1994-306511 A2 19940914
US 1994-346147 A2 19941129
US 1995-497214 A2 19950630
US 1996-581918 A2 19960102

US	1991-701514	A2 19910516
WO	1992-US4146	A 19920518
US	1992-888178	B2 19920526
US	1992-963308	A2 19921016
US	1992-991997	B2 19921217
US	1994-346174	A2 19941129

AB The present invention relates to transgenic mice in which the biol. function of at least one cell cycle regulatory proteins of the INK4 family is altered. In a preferred embodiment, the knockout construct is designed to undergo homologous recombination with an INK4 gene which encodes an INK4 polypeptide characterized by ankyrin-like repeats (e.g., a p16, p15, p18 and/or p19 gene mutated to give rise to a frameshift or a premature stop codon in the coding sequence). The p16 gene is thereby demonstrated to be a tumor suppressor and its inactivation appears to be an important genetic lesion in the development of human cancers. Animals in which an INK4 gene has been disrupted are viable, but develop both spontaneous and induced tumors. Accordingly, the subject transgenic animal may be used to screen for compds which are potential anti-proliferative agents useful for inhibiting growth of such tumors.

IC ICM C12N015-00
ICS C12N015-09; C12N015-63; C12N005-00

NCL 800018000

CC 3-2 (Biochemical Genetics)
Section cross-reference(s): 9, 13, 14, 64

ST transgenic mouse INK4 gene knockout tumor susceptibility; proliferation inhibitor **screening** INK4 gene knockout mouse

IT Gene, animal
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(**c-myc**, cotransformation with; transgenic mice having modified cell-cycle regulation INK4 genes and increased susceptibility to tumor formation)

IT **Drug screening**
(for antiproliferative/**antitumor** agents; transgenic mice having modified cell-cycle regulation INK4 genes and increased susceptibility to tumor formation)

IT Proliferation inhibition
(proliferation inhibitors, **screening** for; transgenic mice having modified cell-cycle regulation INK4 genes and increased susceptibility to tumor formation)

IT **Antitumor** agents
Carcinogens
Cytotoxic agents
(**screening** for; transgenic mice having modified cell-cycle regulation INK4 genes and increased susceptibility to tumor formation)

IT 166433-52-9, Cyclin D1/CDK6 protein kinase 166433-53-0, Cyclin D1-**CDK4** protein kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(p16INK4A protein interaction with; transgenic mice having modified cell-cycle regulation INK4 genes and increased susceptibility to tumor formation)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 16 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:319602 HCAPLUS
DOCUMENT NUMBER: 131:139056
TITLE: Apoptosis and growth inhibition in malignant lymphocytes after treatment with arsenic trioxide at

clinically achievable concentrations

AUTHOR(S): Zhu, Xin-Hua; Shen, Yu-Lei; Jing, Yong-kui; Cai, Xun; Jia, Pei-Ming; Huang, Ying; Tang, Wei; Shi, Gui-Ying; Sun, Yue-Ping; Dai, Jie; Wang, Zhen-Yi; Chen, Sai-Juan; Zhang, Ting-Dong; Waxman, Samuel; Chen, Zhu; Chen, Guo-Qiang

CORPORATE SOURCE: Shanghai Institute of Hematology, Rui-Jin Hospital, Shanghai Second Medical University, Shanghai, 200025, Peop. Rep. China

SOURCE: Journal of the National Cancer Institute (1999), 91(9), 772-778
CODEN: JNCIEQ; ISSN: 0027-8874

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Arsenic trioxide (As2O3) can induce clin. remission in patients with acute promyelocytic leukemia via induction of differentiation and programmed cell death (apoptosis). We investigated the effects of As2O3 on a panel of malignant lymphocytes to det. whether growth-inhibitory and apoptotic effects of As2O3 can be obsd. in these cells at clin. achievable concns. Eight malignant lymphocytic cell lines and primary cultures of lymphocytic leukemia and lymphoma cells were treated with As2O3, with or without dithiothreitol (DTT) or buthionine sulfoximine (BSO) (an inhibitor of glutathione synthesis). Apoptosis was assessed by cell morphol., flow cytometry, annexin V protein level, and terminal deoxynucleotidyl transferase labeling of DNA fragments. Cellular proliferation was detd. by 5-bromo-2'-deoxyuridine incorporation into DNA and flow cytometry and by use of a mitotic arrest assay. Mitochondrial transmembrane potential (.DELTA..psi.m) was measured by means of rhodamine 123 staining and flow cytometry. Protein expression was assessed by western blot anal. or immunofluorescence. Therapeutic concns. of As2O3 (1-2 .mu.M) had dual effects on malignant lymphocytes: 1) inhibition of growth through ATP (ATP) depletion and prolongation of cell cycle time and 2) induction of apoptosis. As2O3-induced apoptosis was preceded by .DELTA..psi.m collapse. DTT antagonized and BSO enhanced As2O3-induced ATP depletion, .DELTA..psi.m collapse, and apoptosis. Caspase-3 activation, usually resulting from .DELTA..psi.m collapse, was not always assocd. with As2O3-induced apoptosis. As2O3 induced PML (promyelocytic leukemia) protein degrdn. but did not modulate expression of cell cycle-related proteins, including cmyc, retinoblastoma protein, cyclin-dependent kinase 4, cyclin D1, and p53, or expression of differentiation-related antigens. Substantial growth inhibition and apoptosis without evidence of differentiation were induced in most malignant lymphocytic cells treated with 1-2 .mu.M As2O3. As2O3 may prove useful in the treatment of malignant lymphoproliferative disorders.

CC 1-6 (Pharmacology)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**c-myc**; apoptosis and growth inhibition in malignant lymphocytes after treatment with arsenic trioxide)

IT **Antitumor** agents
(leukemia; apoptosis and growth inhibition in malignant lymphocytes after treatment with arsenic trioxide)

IT 147014-97-9, **Cyclin-dependent kinase 4**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(apoptosis and growth inhibition in malignant lymphocytes after treatment with arsenic trioxide)

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 17 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:166635 HCAPLUS
DOCUMENT NUMBER: 130:205970
TITLE: Compositions, kits, and methods for effecting adenine nucleotide modulation of DNA mismatch recognition proteins
INVENTOR(S): Fishel, Richard; Gradia, Scott; Acharya, Samir
PATENT ASSIGNEE(S): Thomas Jefferson University, USA
SOURCE: PCT Int. Appl., 165 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9910369	A1	19990304	WO 1998-US17914	19980828
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9891251	A1	19990316	AU 1998-91251	19980828
US 6333153	B1	20011225	US 1998-143571	19980828
US 2002058275	A1	20020516	US 2001-934909	20010822

PRIORITY APPLN. INFO.:

US 1997-57136P	P	19970828
US 1997-66977P	P	19971128
US 1998-93935P	P	19980723
US 1998-143571	A3	19980828
WO 1998-US17914	W	19980828

AB Compns., and products comprising a MutS homolog which binds to a mismatched region of a duplex DNA mol. in the presence of ADP are provided, as are methods of binding MutS homologs to mismatched DNA in the presence of ADP. Heterodimers of hMSH2:hMH6 are demonstrated to act as a mol. switch which is activatable by ADP based on the activity in binding to mismatched duplex DNA, ATPase activity, and function in mismatch repair. The use of MutL homolog derivs. in combination with MutS homologs is also included. Mutations obsd. in hMSH2 affect the interaction of hMSH2 with other MutS homologs and are assocd. with hereditary non-polyposis colon cancer. Purified human MSH5 homolog and its cDNA sequence are also provided. Finally, nonhuman mammals which are nullizygous for both Msh2 and p53 are also provided, as are methods of making and using the same. The compns. of the present invention have applications as diagnostic reagents in deg. whether a compd. affects tumorigenesis, apoptosis, aging, fetal development, and gene expression of p53 and MutS.

IC ICM C07H021-04
ICS C07K014-435; C12Q001-68; C12P019-34
CC 3-4 (Biochemical Genetics)
Section cross-reference(s): 6, 13, 63
IT Adenoma
Carcinoma
Drug screening

Leukemia
Lymphoma
Melanoma
Sarcoma
(adenine nucleotide modulation of DNA mismatch recognition protein MutS and MutL homologs)

IT Gene, animal
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**c-myc**, diagnosis and therapy and expression modulation of; adenine nucleotide modulation of DNA mismatch recognition protein MutS and MutL homologs)

IT Gene, animal
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**cdk4**, diagnosis and therapy and expression modulation of; adenine nucleotide modulation of DNA mismatch recognition protein MutS and MutL homologs)

IT Embryo, animal
(embryogenesis, **screening** for compds. affecting; adenine nucleotide modulation of DNA mismatch recognition protein MutS and MutL homologs)

IT Gene
(expression, **screening** for compds. affecting; adenine nucleotide modulation of DNA mismatch recognition protein MutS and MutL homologs)

IT Nerve, neoplasm
(**neuroblastoma**; adenine nucleotide modulation of DNA mismatch recognition protein MutS and MutL homologs)

IT Aging, animal
Apoptosis
(**screening** for compds. affecting; adenine nucleotide modulation of DNA mismatch recognition protein MutS and MutL homologs)

IT **Antitumor** agents
(**screening** for; adenine nucleotide modulation of DNA mismatch recognition protein MutS and MutL homologs)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 18 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:433904 HCAPLUS
DOCUMENT NUMBER: 129:160009
TITLE: Chromosomal and gene amplification in diffuse large B-cell lymphoma
AUTHOR(S): Rao, Pulivarthi H.; Houldsworth, Jane; Dyomina, Katerina; Parsa, Nasser Z.; Cigudosa, Juan C.; Louie, Diane C.; Popplewell, Leslie; Offit, Kenneth; Jhanwar, Suresh C.; Chaganti, R. S. K.
CORPORATE SOURCE: Cell Biology Program and the Department of Pathology and Human Genetics, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021, USA
SOURCE: Blood (1998), 92(1), 234-240
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Chromosomal translocations leading to deregulation of specific oncogenes characterize approx. 50% of cases of diffuse large B-cell lymphomas (DLBL). To characterize addnl. genetic features that may be of value in delineating the clin. characteristics of DLBL, we studied a panel of 96 cases at diagnosis consecutively ascertained at the Memorial Sloan-Kettering Cancer Center (MSKCC) for incidence of gene amplification,

a genetic abnormality previously shown to be assocd. with tumor progression and clin. outcome. A subset of 20 cases was subjected to comparative genomic hybridization (CGH) anal., which identified nine sites of chromosomal amplification (1q21-23, 2p12-16, 8q24, 9q34, 12q12-14, 13q32, 16p12, 18q21-22, and 22q12). Candidate amplified genes mapped to these sites were selected for further anal. based on their known roles in lymphoid cell and lymphoma development, and/or history of amplification in tumors. Probes for six genes, which fulfilled these criteria, REL (2p12-16), MYC (8q24), BCL2 (18q21), GLI, CDK4, and MDM2 (12q13-14), were used in a quant. Southern blotting anal. of the 96 DLBL DNAs. Each of these genes was amplified (four or more copies) with incidence ranging from 11% to 23%. This anal. is consistent with our previous finding that REL amplification is assocd. with extranodal presentation. In addn., BCL2 rearrangement and/or REL, MYC, BCL2, GLI, CDK4, and MDM2 amplification was assocd. with advanced stage disease. These data show, for the first time, that amplification of chromosomal regions and genes is a frequent phenomenon in DLBL and demonstrates their potential significance in lymphomagenesis.

CC 14-1 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 3

IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(**CDK4**; chromosomal and gene amplification in diffuse large B-cell lymphoma)

IT Proteins, specific or class
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**CDK4**; chromosomal and gene amplification in diffuse large B-cell lymphoma)

IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(**c-myc**; chromosomal and gene amplification in diffuse large B-cell lymphoma)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**c-myc**; chromosomal and gene amplification in diffuse large B-cell lymphoma)

IT Recombination, genetic
(**translocation**; chromosomal and gene amplification in diffuse large B-cell lymphoma)

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=> fil wpids
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     (FILE 'HCAPLUS' ENTERED AT 07:52:37 ON 20 MAY 2002)
               DEL HIS Y

     FILE 'WPIDS' ENTERED AT 07:53:29 ON 20 MAY 2002
               E WO2001059090/PN
L2          102 S CDK4 OR CDK 4 OR CYCLIN DEPENDENT KINASE (2W) 4
L3          193 S C MYC
L4            3 S L2 (L) L3
L5            3 S L2 AND L3
L6          212 S CYCLIN DEPENDENT KINASE#
L7           54 S L6 AND L2
L8            0 S CDK AND L3
L9          907 S TRANSLOCAT? OR MUTAT? (3A) (APC OR CATENIN# )
L10        1845 S BURKITT# OR NEUROBLAST? OR COLON CANCER#
L11        2726 S L9 OR L10
L12           2 S L7 AND L11
L13      200219 S SCREEN?
L14           9 S L7 AND L13
L15       15617 S ANTICANCER# OR ANTITUMOR# OR ANTITUMOUR# OR ANTINEOPLAS?
L16        4831 S (CANCER# OR TUMOR# OR TUMOUR# OR NEOPLAS?)(2A) INHIBIT?
L17          14 S L7 AND L15
L18           9 S L7 AND L16
L19          25 S L12 OR L14 OR L17 OR L18
L20          24 S L19 NOT L5

     FILE 'WPIDS' ENTERED AT 08:06:55 ON 20 MAY 2002

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L20 IS NOT VALID HERE

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L5   ANSWER 1 OF 3  WPIDS (C) 2002 THOMSON DERWENT
```

AN 2001-522472 [57] WPIDS
DNC C2001-155984
TI Reporter construct useful for screening compounds with anti-cancer activity, has upstream region of **CDK4** gene transcription start site, having four **c-MYC** binding sites and a coding sequence for reporter protein.
DC B04 D16
IN HERMEKING, H; KINZLER, K W; VOGELSTEIN, B
PA (UYJO) UNIV JOHNS HOPKINS
CYC 21
PI WO 2001059090 A2 20010816 (200157)* EN 40p
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
W: AU CA
AU 2001038096 A 20010820 (200175)
ADT WO 2001059090 A2 WO 2001-US4227 20010209; AU 2001038096 A AU 2001-38096 20010209
FDT AU 2001038096 A Based on WO 200159090
PRAI US 2000-181930P 20000211
AB WO 200159090 A UPAB: 20011005
NOVELTY - A reporter construct (I) comprising an upstream region (UR) of a mammalian **cyclin dependent kinase 4** (**CDK4**) gene transcription start site comprising at least four **c-MYC** binding sites operably linked to a coding sequence (CS) for a reporter protein, so that a wild-type **c-MYC**, upon binding to UR, activates transcription of CS, is new. (I) comprises UR upstream of CS.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a host cell (II) comprising (I), and a **c-MYC** protein, where the protein binds to (I) and activates transcription of CS;

(2) an isolated and purified nucleic acid molecule (III) comprising at least one copy of a region upstream of a human **CDK4** gene transcriptional start site, where the region comprises at least four **c-MYC** binding sites comprising the sequence CACGTG, where the nucleic acid molecule does not contain the **CDK4** coding sequence;

(3) screening test compounds for anti-cancer activity, by:

(a) contacting a **c-MYC** protein with (I) in the presence of a test compound, and monitoring expression of the reporter protein, where the test compound which decreases expression of the reporter protein is a candidate anti-cancer agent;

(b) contacting a **c-MYC** protein with (III) in the presence of a test compound, and monitoring binding of **c-MYC** protein to the nucleic acid molecule, where a test compound which decreases binding of **c-MYC** to the nucleic acid molecule is identified as a candidate anti-cancer agent; or

(c) contacting a cell which has a genetic alteration which dysregulates **c-MYC** expression with a test compound, and measuring activity of **CDK4** in the cell, where a test compound which inhibits activity of **CDK4** is identified as a candidate agent with anti-cancer activity;

(4) inhibiting the growth of tumor cells, by contacting tumor cells comprising a genetic alteration which causes **c-MYC** over expression with an agent (A) which inhibits **CDK4** enzymatic activity, such that the tumor cell growth is inhibited; and

(5) determining responsiveness to an anti-cancer agent which inhibits **CDK4** activity, by testing a cancer cell for the presence of a mutation such as t8;14 translocation, APC mutation, amplification of **c-MYC**, and a beta -catenin mutation, where the cancer cell which is identified as having the mutation is identified as being

susceptible to an inhibitor of **CDK4**.
ACTIVITY - Cytostatic.
MECHANISM OF ACTION - Inhibitor of **CDK4** enzymatic activity.
No supporting data given.
USE - (I) And (III) are useful for screening compounds with anti-cancer activity (claimed).
(I) and (II) are useful for drug screening and identification. The agents that are screened are useful for inhibiting tumor cell growth in vitro or in vivo.
Dwg.0/5

TECH UPTX: 20011005
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Construct: (I) Comprises UR (of at least 200 bp) of human **CDK4** transcription start site comprising at least four **c-MYC** sites containing CACGTG motifs. (III) is attached to a solid support.
Preferred Method: (I) And **c-MYC** protein are in a host cell and the test compound is contacted with the host cell. The cell has a t8;14 translocation, APC mutation (truncation mutation) or genetic amplification of **c-MYC**. (I) and **c-MYC** protein are contacted in a cell-free transcription/translation system. The method further involves administering to the cancer cell, e.g. tumor cells selected from Burkitt's Lymphoma cells, neuroblastoma cells and colon cancer cells, an anti-cancer agent which inhibits **CDK4** activity. (A) is p16 or a polypeptide comprising a truncated version of p16.

L5 ANSWER 2 OF 3 WPIDS (C) 2002 THOMSON DERWENT
AN 2000-524218 [47] WPIDS
DNN N2000-387494 DNC C2000-155662
TI Composition for delivery of a virus vector to an animal cell comprising a virus vector bound to the exterior surface of a matrix, useful for gene therapy of conditions such as cancer and wounds.
DC A96 B04 B07 D16 D22 P31
IN JONES, P L; LEVY, R J
PA (CHIL-N) CHILDRENS HOSPITAL PHILADELPHIA
CYC 90
PI WO 2000043044 A1 20000727 (200047)* EN 83p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000034714 A 20000807 (200055)
ADT WO 2000043044 A1 WO 2000-US1193 20000119; AU 2000034714 A AU 2000-34714 20000119
FDT AU 2000034714 A Based on WO 200043044
PRAI US 1999-116405P 19990119
AB WO 200043044 A UPAB: 20000925
NOVELTY - A composition for delivery of a virus vector to an animal cell comprising a virus vector bound to the exterior surface of a matrix in a physiologically reversible manner, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) a surface coated with the composition above;
(2) an implantable device having a surface coated with the composition;
(3) a method (M1) of making a composition for delivery of a virus vector to an animal; and
(4) a method (M2) of delivering a virus vector to an animal tissue,

comprising placing the composition in fluid communication with the animal tissue.

ACTIVITY - Vulnerary; cytostatic; vasotropic.

MECHANISM OF ACTION - Gene therapy.

USE - The composition is used to deliver nucleic acids encoding anti-restenotic and, anti-oncogenic proteins into cells, particularly in gene therapy of disorders such as wounds, cancer and restenosis.

Dwg.0/1

TECH UPTX: 20000925

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Composition: The matrix is biodegradable and has an internal portion comprising the virus vector bound to the matrix in a physiologically reversible manner. The matrix is not biodegradable and the virus vector is bound to the matrix in a physiologically reversible manner. The composition further comprises a virus-binding agent at the exterior surface, where the virus vector is bound to the virus-binding agent. The matrix is biodegradable and has an internal portion comprising the virus vector bound to the virus-binding agent in a physiologically reversible manner. The virus vector has a net charge, and the virus-binding agent has a second net charge opposite the net charge of the virus vector. The virus-binding agent is selected from a polycation, a polyanion, a cross-linking compound, a polypeptide which specifically binds with the virus vector, the protein or ligand of a specifically-binding protein-ligand pair. The polycation is selected from polylysine, polyarginine, polyornithine, polyhistidine, myelin basic protein, a low molecular weight glycopeptide, a cationic amphiphilic alpha-helical oligopeptide having a repeating sequence, a histone, a galactosylated histone, polybrene, spermine, spermidine, prolamine, polyethylenimine, putrescine, cadaverine, and hexamine. The polycation is poly-L-lysine. The polyanion is a nucleic acid. The cross-linking compound is selected from a di-sulfhydryl compound, SPDP (not defined), a dialdehyde compound, and glutaraldehyde. The polypeptide which specifically binds with the virus vector is selected from an antibody which specifically binds with the virus vector, a fragment of which specifically binds with the virus vector, and a virus receptor protein. The specifically-binding protein-ligand pair is selected from biotin and an avidin, an antibody and an epitope to which the antibody specifically binds, and a viral coat protein and a cell-surface molecule with which the viral coat protein specifically binds. The matrix is selected from a charged biocompatible material, a biocompatible polymer, a biodegradable polymer, a biocompatible biodegradable polymer, polylactic acid, polyglycolic acid, polycaprolactone, a copolymer of polylactic acid and polyglycolic acid, a copolymer of polylactic acid and polycaprolactone, a copolymer of polyglycolic acid and polycaprolactone, a polygylcolide, a polyanhydride, a polyacrylate, a polyalkyl cyanoacrylate, n-butyl cyanoacrylate, isopropyl cyanoacrylate, a polyacrylamide, a polyorthoester, a polyphosphazene, a polypeptide, a polyurethane, a polystyrene, a polystyrene sulfonic acid, a polystyrene carboxylic acid, a polyalkylene oxide, a polyethylene, a polyvinyl chloride, a polyamide, a nylon, a polyester, a rayon, a polypropylene, a polyacrylonitrile, an acrylic, a polyisoprene, a polybutadiene, a polybutadiene-polyisoprene copolymer, a neoprene, a nitrile rubber, a polyisobutylene, an olefinic rubber, an ethylene-propylene rubber, an ethylene-propylene-diene monomer rubber, a polyurethane elastomer, a silicone rubber, a fluoroelastomer, a fluorosilicone rubber, a vinyl acetate homopolymer, a vinyl acetate copolymer, an ethylene vinyl acetate copolymer, an acrylates homopolymer, an acrylates copolymer, polymethylmethacrylate, polyethylmethacrylate, polymethacrylate, ethylene glycol dimethacrylate, ethylene dimethacrylate, hydroxymethyl methacrylate, a polyvinylpyrrolidone, a polyacrylonitrile butadiene, a polycarbonate, a polyamide, a fluoropolymer, polytetrafluoroethylene, polyvinyl fluoride, a polystyrene, a styrene

acrylonitrile homopolymers, a styrene acrylonitrile copolymer, a cellulose acetate, an acrylonitrile butadiene styrene homopolymer, an acrylonitrile butadiene styrene copolymer, a polymethylpentene, a polysulfone, a polyester, a polyimide, a polyisobutylene, a polymethylstyrene, an alginate, an agarose, a dextrin, a dextran, a multi-block polymer, a biocompatible metal alloy, titanium, platinum, stainless steel, hydroxyapatite, tricalcium phosphate, cocoa butter, a wax, and a ceramic material. The matrix comprises a biodegradable polylactate/polyglycolate copolymer and is not electrically conductive. The matrix is in a form selected from a bulk material, a particle, a microsphere, a nanosphere, a device, a coating on a surface of a bulk material, a coating on a surface of a particle, a coating on a surface of a microsphere, a coating on a surface of a nanosphere, and a coating on a surface of a device. The virus vector comprises a transfection indicator. The transfection indicator is selected from the group consisting of a nucleic acid, a nucleic acid analog, a transcription construct, an antisense OGN, a ribozyme, and an expression construct. The transfection indicator is selected from an expression construct encoding a wound healing therapeutic protein, an expression construct encoding an anti-restenotic protein, an expression construct encoding an anti-oncogenic protein, an anti-restenotic antisense OGN, and an anti-oncogenic antisense OGN. The wound healing therapeutic protein is selected from the group consisting of TGF (transforming growth factor)-beta, FGF (not defined), PDGF (platelet derived growth factor), PDGF-beta, IGF (insulin-like growth factor), M-CGF (not defined), BMP (not defined), GH (growth hormone), and PTH (not defined). The anti-restenotic protein is selected from TPA (tissue plasminogen activator), TGF-beta, FGF, Rb, p21, and TK. The anti-oncogenic protein is encoded by a gene selected from abl, akt2, apc, bcl2a, bcl2fl, bcl3, bcr, brca1, brca2, cbl, ccnd1, **cdk4**, crk-II, csj7r/fins, dbl, dcc, dpc4/smad4, ecad, e2f1/rbap, egfr/erbb-1, elk1, elk3, eph, erg, ets1, ets2, fer, fgr/src2,fli1/ergb2, fos, fps/fes, fra1, fra2, fyn, hck, hek, her2/erbb-2lneu, her3/erbb-3, her4/erbb-4, hras1, hst2, hstf1, ink4a, ink4b, int2/fgC, jun, junb, jund, kip2, kit, kras2a, kras2b, lck, lyn, mas, max, mcc, met, mlh1, mos, msh2, msh3, msh6, myb, myba,.mybb, myc, mycl1, mycn, nf1, nf2, nras, p53, pdgfb, pim1, pms1, pms2, ptc, pten, raf1, rb1, rel, ret, ros1, ski, src1, tal1, tgfbr2, thra1, thrb, tiam1, trk, vav, vhl, waf1, wnt1, wnt2, wt1, and yes1. The anti-restenotic antisense oligonucleotide (OGN) is selected from a c-myb antisense OGN, a **c-myc** antisense OGN, and a PCNA antisense OGN. The anti-oncogenic antisense OGN is selected from an OGN based on the genes given above, e.g. an abl antisense OGN, an ets2 antisense OGN. The virus vector is selected from an adenovirus vector, a retrovirus vector, an adeno-associated virus vector (AAV), and a herpes virus vector. The virus vector is an adenovirus vector.

Preferred Device: The device is selected from a wound dressing, a suture, a particle, a vascular stent, and a bulk material. The device is a vascular stent, where the matrix is a polylactate/polyglycolate copolymer comprising polylysine at the exterior surface, where the virus vector is bound with the polylysine, and where the virus vector comprises a transfection indicator selected from an expression construct encoding an anti-restenotic protein and an anti-restenotic antisense OGN.

The device is a suture, where the matrix is a polylactatelpolyglycolate copolymer comprising polylysine at the exterior surface, where the virus vector is bound with the polylysine, and where the virus vector comprises an expression construct encoding a wound healing protein. The device is a particle, where the matrix is a polylactatelpolyglycolate copolymer comprising polylysine at the exterior surface, where the virus vector is bound with the polylysine, and where the virus vector comprises a transfection indicator selected from an expression construct encoding a wound healing therapeutic protein, an expression construct encoding an

anti-restenotic protein, an expression construct encoding an antioncogenic protein, an anti-restenotic antisense OGN, and an anti-oncogenic antisense OGN. The particle has a diameter less than 900 micrometers, preferably less than 1 micrometer.
The device is a bulk material, where the matrix is a polylactate/polyglycolate copolymer comprising polylysine at the exterior surface, where the virus vector is bound with the polylysine, and where the virus vector comprises a transfection indicator selected from an expression construct encoding a wound healing therapeutic protein, an expression construct encoding an anti-restenotic protein, an expression construct encoding an anti-oncogenic protein, an anti-restenotic antisense OGN, and an anti-oncogenic antisense OGN. The device is selected from a wound dressing, a suture, a particle, a vascular stent, and a bulk material.
Preferred Method: In M1 the matrix comprises a virus-binding agent at the exterior surface. The matrix is biodegradable and is on the surface of an implantable device. A suspension comprising the matrix and a solvent is applied to the surface of the implantable device and the solvent is removed from the surface prior to contacting the virus vector with the matrix. The suspension further comprises the virus-binding agent. A precursor composition comprising a number of monomers of the polymer is applied to the surface of the implantable device and the monomers are polymerized prior to contacting the virus vector with the matrix. The precursor composition further comprises the virus-binding agent.
In M2 the composition further comprises a virus-binding agent at the exterior surface, and the virus vector is bound to the virus-binding agent. The composition is placed in contact with the animal tissue. The animal tissue is outside of the body of the animal from which it was obtained. The animal tissue is in an animal. Placing the composition in fluid communication with the tissue comprises placing an implantable device having a surface coated with the composition. The device is selected from a wound dressing, a suture, a particle, a vascular stent, and a bulk material. The tissue is selected from a wounded tissue, an ischemic tissue, a gastrointestinal tissue, an embryonic tissue, and a fetal tissue.

L5 ANSWER 3 OF 3 WPIDS (C) 2002 THOMSON DERWENT
AN 1999-329399 [28] WPIDS
DNC C1999-097657
TI Oncogene- or virus-regulated system for expressing effector gene, used to treat or prevent e.g. cancer, viral infections and autoimmune disease.
DC B04 D16
IN MULLER, R; SEDLACEK, H; MUELLER, R
PA (HMRI) HOECHST MARION ROUSSEL DEUT GMBH
CYC 34
PI EP 922768 A2 19990616 (199928)* DE 44p
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
CZ 9803768 A3 19990616 (199929)
AU 9893256 A 19990610 (199934)
DE 19751587 A1 19990729 (199936)
CN 1221033 A 19990630 (199944)
CA 2251257 A1 19990521 (199945) EN
BR 9804720 A 20000328 (200029)
JP 2000106886 A 20000418 (200030) 27p
KR 99045475 A 19990625 (200036)
MX 9809698 A1 19990601 (200058)
HU 9802681 A1 20001030 (200064)
ADT EP 922768 A2 EP 1998-121471 19981111; CZ 9803768 A3 CZ 1998-3768 19981119; AU 9893256 A AU 1998-93256 19981119; DE 19751587 A1 DE 1997-19751587

19971121; CN 1221033 A CN 1998-122537 19981120; CA 2251257 A1 CA 1998-2251257 19981119; BR 9804720 A BR 1998-4720 19981120; JP 2000106886 A JP 1998-333200 19981124; KR 99045475 A KR 1998-50050 19981121; MX 9809698 A1 MX 1998-9698 19981119; HU 9802681 A1 HU 1998-2681 19981119

PRAI DE 1997-19751587 19971121

AB EP 922768 A UPAB: 19990719

NOVELTY - Nucleic acid construct (A) comprises a promoter for expressing an effector gene (I), and a promoter for regulating expression of transcription factor gene (II), where protein (II) binds the promoter of (I) to control expression. The activity of the protein (II) depends on cellular regulatory protein(s) which specifically bind to and modify its activity.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) vector containing (A); and

(2) isolated cells containing (A) or the vector.

ACTIVITY - Antiviral; antibacterial; antitumor; anti-allergic; anti-arthritic; anti-anemic.

MECHANISM OF ACTION - Cell-specific expression of inserted gene.

USE - (A) (also vectors and cells containing them) are used for treatment and prevention of infections (bacterial or viral), tumors, leukemia, autoimmune disease, allergy, arthritis, inflammation, organ rejection. guest vs. host disease, blood coagulation or circulatory disorders, anemia, hormonal disorders and central nervous system injury.

ADVANTAGE - (A) are activated, and thus cause expression of (II) only in cells where a particular regulatory protein is present at a reduced level or in an altered form, i.e. they provide cell-specific expression.

Dwg.0/3

TECH UPTX: 19990719

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred constructs: These are of two basic types:

(1) consisting of an activating sequence (a) for transcription of a transcription factor (b), that comprises activation domain (b1), binding domain for cell regulatory protein (b2) and DNA-binding domain (b3); (c) an activating sequence activated by binding of the (b) expression product, thus causing activation of (I); and

(2) consisting of activating sequence (a') comprising a DNA-binding sequence (a1) for a cellular regulatory protein and basal promoter (a2), (b') a transcription factor, i.e. a repressor protein that inhibits component (c'), which is an activating sequence comprising an activator (c1) of transcription of (I) and a DNA sequence (c2) that binds the repressor so as to inhibit transcription of (I).

In (1), components (a) and (c) are particularly the same, and (a) and (c1) are non-specific, cell-specific, metabolically specific, virus-specific and/or cell-cycle specific promoters, typically activated in endothelial, peritoneal or epithelial cells, viral promoters, promoters or enhancers activated by hypoxia, etc.

(b1) is an activating domain from the transcription factors Oct-2, Sp1, NFY, ITF-2, VP-16, **c-Myc** or CTF, and (b2) is (part of) a cellular binding protein that binds to cellular regulatory proteins such as p53, pRb, **cdk4**, etc. Alternatively, (b2) is:

(i) at least part of a viral binding protein (binding to p53, pRb. NFkappaB etc.), e.g. Epstein-Barr nuclear antigens, Tax from human immune deficiency virus (HIV)-1, E6 from human papilloma virus etc.; or

(ii) an antibody or its fragment.

(c) contains at least one DNA binding sequence for the Gal4, LexA, Lac I-repressor, tetracyclin repressor or ZFHD-1 proteins. (a1) is p53, W4-1, NF-kappaB, E2F/DP or Myc/Max protein, and (a2) is one of the basal promoters SV40, c-fos, U2sn RNA and herpes simplex thymidine kinase, in which case the repressor is the lac or tetracyclin repressor gene, and the

binding site for the repressor contains at least one lac- or tetracyclin-operator binding sequences.
(I) encodes a cytokine, chemokine, growth factor (or their receptors); antiproliferative, cytostatic or apoptotic agents; antibodies; angiogenesis inhibitors; hormones; coagulation factors etc; antigens (from pathogens or tumors); prodrug-converting enzyme; ribozyme or antisense RNA. The disclosure lists many suitable (I), together with appropriate promoters and target tissues. Several (I), or transcription factor genes, may be present in (A), separated by internal ribosome entry sites.
Preferred vectors: These are viral or plasmid vectors.

L20 ANSWER 1 OF 24 WPIDS (C) 2002 THOMSON DERWENT
AN 2002-083072 [11] WPIDS
DNN N2002-061885 DNC C2002-025207
TI New genetic variants comprising haplotypes of the **cyclin-dependent kinase 4** (**CDK4**) gene, useful in improving the efficiency drug **screening** protocols for compounds targeting **CDK4**.
DC B04 D16 T01
IN DUDA, A E; KAZEMI, A; KOSHY, B; SAUSKER, E A
PA (GENA-N) GENAISSANCE PHARM INC
CYC 94
PI WO 2001090115 A2 20011129 (200211)* EN 58p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001074874 A 20011203 (200221)
ADT WO 2001090115 A2 WO 2001-US16350 20010518; AU 2001074874 A AU 2001-74874 20010518
FDT AU 2001074874 A Based on WO 200190115
PRAI US 2000-205867P 20000519
AB WO 200190115 A UPAB: 20020215
NOVELTY - An isolated polynucleotide (I) comprising fragments and haplotypes of the **cyclin-dependent kinase 4** (**CDK4**) gene is new. The polynucleotide comprises polymorphic sites referred to as PS1-6 to designate the order in which they are located in the gene.
DETAILED DESCRIPTION - (I) comprises a nucleotide sequence selected from:
(a) a first nucleotide sequence, which comprises a **CDK4** isogene, where the **CDK4** isogene is selected from isogenes 1-3 and 5-6 fully described in the specification and where each of the isogenes comprise the regions of the sequence having 4233 base pairs (II) fully defined in the specification and where each of the isogenes 1-3 and 5-6 is further defined by the corresponding set of polymorphisms whose locations and polymorphisms are fully described in the specification;
(b) a second nucleotide sequence which comprises a fragment of the first nucleotide sequence, where the fragment comprises one or more polymorphisms consisting of adenine at PS1, guanine at PS2, guanine at PS3, cytosine at PS4, cytosine at PS5 and adenine at PS6; and
(c) a third nucleotide sequence, which is complementary to the first or second nucleotide sequence.
(I) may alternatively comprise a nucleotide sequence selected from:
(a) a coding sequence for an **CDK4** isogene selected from

coding sequences 1-3 and 5-6 fully defined in the specification and where each of the coding sequences 1-3 and 5-6 comprises the 912 base pairs fully defined in the specification, except at each of the polymorphic sites (PS) which have the locations and polymorphisms fully described in the specification; and

(b) a fragment of the coding sequence, where the fragment comprises at least one polymorphism consisting of guanine at a position corresponding to nucleotide 477 and adenine at a position corresponding to nucleotide 696.

INDEPENDENT CLAIMS are also included for:

(1) haplotyping the **CDK4** gene of an individual;

(2) genotyping the **CDK4** gene of an individual;

(3) predicting a haplotype pair for the **CDK4** gene of an individual;

(4) identifying an association between a trait and at least one haplotype or haplotype pair of the **CDK4** gene;

(5) a composition comprising at least one genotyping oligonucleotide for detecting a polymorphism in the **CDK4** gene at a polymorphic site consisting of PS1, PS2, PS3, PS4, PS5 and PS6, where the selected PS have the location and alternative alleles shown in (I);

(6) recombinant nonhuman organisms transformed or transfected with the isolated polynucleotide, where the organism expresses an **CDK4** protein encoded by the first nucleotide sequence or an **CDK4** protein encoded by the polymorphic variant sequence;

(7) a computer system for storing and analyzing polymorphism data for the **CDK4** comprising:

(a) a central processing unit (CPU);

(b) a communication interface;

(c) a display device;

(d) an input device; and

(e) a database containing the polymorphism data; and

(8) a genome anthology for the **CDK4** gene, which comprises **CDK4** isogenes defined by any one of haplotypes 1-6 fully defined in the specification.

USE - The polymorphisms and haplotypes of **CDK4** gene are useful for validating whether **CDK4** is a suitable target for drugs to treat cancer and disorders associated with impaired protein synthesis in cells, **screening** for such drugs and reducing bias in clinical trials of such drugs. Haplotype information would be useful in improving the efficiency and output of several steps in the drug discovery and development process, including target validation, identifying lead compounds, early phase clinical trials. The methods are useful in **screening** for compounds targeting **CDK4** to treat a specific condition or disease predicted to be associated with **CDK4** activity.

ADVANTAGE - The methods of the invention take into account that natural genetic variability exists between individuals in any and every population with respect to pharmaceutically-important proteins, including the protein targets of candidate drugs, the enzymes that metabolize these drugs and the proteins whose activity is modulated by such drug targets.

Dwg.0/3

TECH UPTX: 20020215

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Polynucleotide: The isolated polynucleotide is a DNA molecule and comprises both the first and third nucleotide sequence. It further comprises expression regulatory elements operably linked to the first nucleotide sequence. The isolated polynucleotide may also consists of the second nucleotide sequence. Preferred Method: In method (1), haplotyping the **CDK4** gene of an individual comprises determining which of the **CDK4** haplotypes defined in found in the repository for the **CDK4** gene defines one

copy of the individual's **CDK4** gene. The determining step comprises identifying the phased sequence of nucleotides present at each of PS1-6 on the one copy of the individual's **CDK4** gene.
Haplotyping the **CDK4** gene an individual also comprises determining which of the **CDK4** haplotype pairs found in the repository for the **CDK4** gene defines both copies of the individual's **CDK4** gene. The determining step comprises identifying the phased sequence of nucleotides present at each of PS1-6 on both copies of the individual's **CDK4** gene. Haplotyping the **CDK4** gene of an individual also comprises determining for one copy of the **CDK4** gene present in the individual, the identity of the nucleotide at two or more polymorphic sites (PS) consisting of PS1, PS2, PS3, PS4, PS5 and PS6, where the selected PS have the location and alternative alleles shown in (II). In method (2), genotyping the **CDK4** gene of an individual comprises determining for the two copies of the **CDK4** gene present in the individual the identity of the nucleotide pair at one or more polymorphic sites (PS) selected from PS1, PS2, PS3, PS4, PS5 and PS6, where the one or more PS have the location and alternative alleles shown in (I). The determining step comprises:
(a) isolating from the individual a nucleic acid mixture comprising both copies of the **CDK4** gene, or its fragment, that are present in the individual;
(b) amplifying from the nucleic acid mixture a target region containing the selected polymorphic site;
(c) hybridizing a primer extension oligonucleotide to one allele of the amplified target region;
(d) performing a nucleic acid template-dependent, primer extension reaction on the hybridized genotyping oligonucleotide in the presence of at least two different terminators pf the reaction, where the terminators are complementary to the alternative nucleotides present at selected polymorphic site; and
(e) detecting the presence and identity of the terminator in the extended genotyping oligonucleotide.
The method also comprises determining for the two copies of the **CDK4** gene present in the individual the identity of the nucleotide pair at each of PS1-6.
In method (3), predicting a haplotype pair for the **CDK4** gene of an individual comprises:
(a) identifying an **CDK4** genotype for the individual, where the genotype comprises the nucleotide pair at two or more polymorphic sites (PS) comprising PS1, PS2, PS3, PS4, PS5 and PS6;
(b) enumerating all possible haplotype pairs, which are consistent with the genotype;
(c) comparing the possible haplotype pairs to the haplotype pair data found in the Index Repository for PS1-6 and the human genotypes and haplotypes found in the repository for the **CDK4** gene fully described in the specification; and
(d) assigning a haplotype pair to the individual that is consistent with the data.
The identified genotype of the individual comprises the nucleotide pair at each of PS1-6. In method (4), identifying an association between a trait and at least one haplotype or haplotype pair of the **CDK4** gene comprises comparing the frequency of the haplotype or haplotype pair in a population exhibiting the trait with the frequency of the haplotype or haplotype pair in a reference population. A higher frequency of the haplotype or haplotype hair in the trait population than in the reference population indicates the trait is associated with the haplotype or haplotype pair. In particular, trait is a clinical response to a drug targeting **CDK4**.

Preferred Composition: The genotyping oligonucleotide is an allele-specific oligonucleotide that specifically hybridizes to an allele of the **CDK4** gene at a region containing the polymorphic site. The allele-specific oligonucleotide comprises a nucleotide sequence consisting of:
(a) any of 6 sequences fully defined in the specification, e.g. ttaaaggrga ttgaa; tggtgacrag tggtg; gttgggarta ggaga; ggctcaasca gtcct; gttggccytt attcc; or ttgggctrcc tccag;
(b) the complements of (a); or
(c) any of 12 sequences fully defined in the specification, e.g. gttgggttaa aggrg; tcacttttca atcyc; acattctggt gacra; ctgttccacc actyg; gttctggttg ggart; aatcactctc ctayt; ctcctgggct caasc; ggtgagagga ctgst; ggaattgttg gccyt; gtatagggaa taarg; gcctgattgg gctrc; or catcctctgg aggya.
The genotyping oligonucleotide is a primer-extension oligonucleotide, which comprises any of 12 nucleotide sequences fully defined in the specification, e.g.: gggttaaagg; or cttttcaatc.
Preferred Organism: The recombinant organism is preferably a nonhuman transgenic animal.

L20 ANSWER 2 OF 24 WPIDS (C) 2002 THOMSON DERWENT
AN 2002-066513 [09] WPIDS
DNC C2002-019820
TI New 3-hydroxychromen-4-one derivatives are **cyclin dependent kinase** inhibitors, useful for treating cancer and diseases induced by cell proliferation, e.g. inflammation, angiogenesis.
DC B02
IN CHOI, S H; CHUNG, H H; HONG, C Y; JEONG, S W; KIM, D M; KIM, E E K; KIM, J H; LEE, J H; PARK, T S; RO, S G; SON, H S; YOON, S K
PA (GLDS) LG CHEM INVESTMENT LTD
CYC 93
PI WO 2001083469 A1 20011108 (200209)* EN 103p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001055090 A 20011112 (200222)
ADT WO 2001083469 A1 WO 2001-KR725 20010503; AU 2001055090 A AU 2001-55090 20010503
FDT AU 2001055090 A Based on WO 200183469
PRAI KR 2000-54577 20000918; KR 2000-23705 20000503; KR 2000-54573 20000918
AB WO 200183469 A UPAB: 20020208
NOVELTY - 3-Hydroxychromen-4-one derivatives (I) are new.
DETAILED DESCRIPTION - 3-Hydroxychromen-4-one derivatives of formula (I), and their salts, hydrates, solvates and isomers, are new
A = H; NO2; amino optionally substituted by 1-4C alkylcarbonyl or carbamoyl; or a group of formula (i)-(iv):
R4 = H or 1-6C alkyl optionally substituted by NH2 or OH;
R3 = 1-6C alkyl optionally substituted by NH2 or OH;
D = halo;
B = Me; or amino optionally substituted by 1 or 2 1-6C alkyl, hydroxy (1-6C alkyl), 3-6C cycloalkyl, acetyl, phenyl, benzyl or piperidinyl;
X, Y, Z = H; OH; NO2; CN; halo; amino optionally substituted by 1-4C alkyl, 1-4C alkylcarbonyl or carbamoyl; or 1-4C alkyl optionally substituted by OH or halo.
An INDEPENDENT CLAIM is included for the preparation of (I).

ACTIVITY - Cytostatic; antiinflammatory.
MECHANISM OF ACTION - CDK inhibitors.
In tests to determine CDK2 and **CDK4** inhibitory activity, 8-amino-2-(3-amino-4-hydroxyphenyl)-3-hydroxy-6-methyl-4H-chromen-4-one had IC50 values 1.4 and 20.0 micro M respectively.
USE - For suppression and treatment of cancer and diseases induced by cell proliferation, e.g. inflammation, angiostenosis or angiogenesis. (I) may be administered with other **anticancer** agents.
Dwg.0/0

TECH UPTX: 20020208
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) can be prepared e.g. by:
(i) reacting a phenol of formula (II) with an aldehyde of formula (III) to give (IV); and cyclizing (IV) in the presence of a base to give (I);
(ii) (a) reacting an amine of formula (V) with 3-chloropropanesulfonylchloride in the presence of a base and a catalyst; and (b) deprotecting the product from (a) to give (IA).
P = a protecting group;

L20 ANSWER 3 OF 24 WPIDS (C) 2002 THOMSON DERWENT
AN 2002-043183 [06] WPIDS
DNN N2002-032064 DNC C2002-012488
TI Measuring **cyclin-dependent kinase** (CDK) activity by measuring amount of CDK-phosphorylated retinoblastoma protein (Rb) in sample by quantitating anti-Rb primary antibody (AbP) in antiRb capture antibody-Rb-AbP complex.
DC B04 D16 S03
IN FOSTER, B A; RASTINEJAD, F
PA (PFIZ) PFIZER PROD INC
CYC 26
PI EP 1156332 A2 20011121 (200206)* EN 12p
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
ADT EP 1156332 A2 EP 2001-303854 20010427
PRAI US 2000-205932P 20000428
AB EP 1156332 A UPAB: 20020128
NOVELTY - Measuring, (M1), **cyclin-dependent kinase** (CDK) activity in a sample comprising contacting the sample with an anti-retinoblastoma protein (Rb) capture antibody (Ab) and isolating Ab-Rb complex; contacting the complex with an anti-Rb primary antibody (AbP), isolating Ab-Rb-AbP complex; and measuring the amount of CDK-phosphorylated Rb in the sample by quantitating AbP in Ab-Rb-AbP complex, is new.
USE - (M1) is useful for measuring human CDK activity in a sample. The method is useful for identifying an agent that modulates CDK activity in a cell, where the sample is cell lysate contacted with an agent, and agent modulates CDK activity if the amount of CDK phosphorylated Rb differs from a control cell not exposed to the agent. The method identifies an agent that decreases CDK activity which is useful for treatment of a disease or condition that is improved by inhibiting cellular proliferation such as cancers, autoimmune diseases, viral diseases, fungal diseases, degenerative disorders, cardiovascular diseases, stroke, inflammatory disorders, and dermatological disorders; or identifies an agent that increases CDK activity which is useful for treatment of a disease or condition that is improved by increasing cellular proliferation such as neurodegeneration, to stimulate wound healing or stimulate immune system activity (claimed) as well as in other disease and conditions in which the inhibition of cellular proliferation is beneficial which include tumors of the central and peripheral nervous system. These inhibitors CDK inhibitors could act as reversible cytostatic

agents which may be useful in the treatment of any disease or condition associated with abnormal or deleterious cellular proliferation, such as Kaposi's sarcoma, benign prostate hyperplasia, familial adenomatosis polyposis, neurofibromatosis, atherosclerosis, thrombotic microangiopathy syndromes, pulmonary fibrosis, arthritis, psoriasis, restenosis following angioplasty or vascular surgery, hypertrophic scar formation, inflammatory bowel disease, transplantation rejection, endotoxic shock, mesangial cell proliferative disorders (including glomerulonephritis), diabetic nephropathy, glomerulopathies, malignant nephrosclerosis, organ transplant rejection, macular degeneration, fungal infections and viral infections.

ADVANTAGE - (M1) provides information regarding the level of intracellular CDK activity and provides more physiologically relevant information on CDK activity than conventional methods, which typically analyze in vitro CDK activity. Therefore, the method is useful when studying changes in intracellular CDK activity over the course of the cell cycle or to identify compounds that modulate CDK activity in cultured cells or in animals. The identification of novel CDK inhibitors also provides the benefit of creating a pool of cell cycle regulators that can be used to modulate cellular proliferation. When used as **antitumor** agents, the CDK inhibitors generate little risk of secondary tumor development because they lack direct DNA interaction; the CDK inhibitors provide candidate therapies to treat conditions (e.g. viral infections), in which CDK activity is not misregulated but is nonetheless essential for maintenance of the condition; and the inhibitors may be used to protect normal cells from the toxicity of cycle specific chemotherapeutic agents which occurs in S-phase, G2 or mitosis, by preventing cell cycle progression in the normal cells.

Dwg.0/1

TECH UPTX: 20020128

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: In (M1), CDK is preferably CDK2 or **CDK4**, and the method measures intracellular CDK activity preferably in a cultured cell or measures ex vivo CDK activity in a cell taken from an animal. Ab is preferably bound to a test plate.

L20 ANSWER 4 OF 24 WPIDS (C) 2002 THOMSON DERWENT
AN 2001-502601 [55] WPIDS
DNC C2001-151171
TI New pseudopolymorph Form I of flavopiridol is **cyclin dependent kinase** inhibitor used for treating cancers, leukemia and lymphoma.
DC B02
IN BAFUS, G L; HARRISON-BOWMAN, C M; SILVEY, G L
PA (AVET) AVENTIS PHARM INC
CYC 94
PI WO 2001053293 A1 20010726 (200155)* EN 23p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001026346 A 20010731 (200171)
ADT WO 2001053293 A1 WO 2001-US519 20010108; AU 2001026346 A AU 2001-26346 20010108
FDT AU 2001026346 A Based on WO 200153293
PRAI US 2000-484717 20000118
AB WO 200153293 A UPAB: 20010927
NOVELTY - Pseudopolymorph Form I of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8(4R-(3S-hydroxy-1-methyl)piperidinyl)-4H-1-benzopyran-4-one

(flavopiridol) having an X-ray powder diffraction pattern expressed in terms of D spacing comprising 12.708, 4.323, 5.594, 5.349, and 3.590 A deg. , is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) preparation of Form 1, and

(2) a form of flavopiridol or flavopiridol hydrochloride having a weight gain due to water of upto 5% at a relative humidity of 75%.

ACTIVITY - Cytotoxic; immunomodulator; antiinflammatory.

MECHANISM OF ACTION - Protein kinase inhibitor; **cyclin dependent kinase** (CDK) inhibitor; CDK1, CDK2, **CDK4**, CDK6, and CDK7 inhibitor.

No biological data is given.

USE - Flavopiridol is an Immunomodulator and antiinflammatory agent (see US4900127). Pseudopolymorph Form I is used for treating cancer (claimed), e.g. leukemia, mesothelioma, and cancers of the lung, colorectal, breast, ovarian, prostate melanoma, renal, uterine body and central nervous system.

ADVANTAGE - The Form I is less hydroscopic than the Form II, e.g. it has less weight gain due to water in comparative relative humidity environments.

Dwg.0/1

TECH UPTX: 20010927

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred compounds: The pseudopolymorph Form I has an X-ray diffraction pattern expressed in terms of D spacing and relative intensities of 12.708 (100%), 4.323 (75.9%) and 5.594 (58.5%) Adegrees; and 5.349 (49.5%), 3.590 (46.6%), 3.366 (42.0%), 4.209 (40.7%), 3.395 (39.5%), 3.438 (38.8%) and 4.839 (37.1%) Adegrees. The compounds are also characterized by 2theta angle (degrees), D space-Adegrees, relative intensity and relative intensity (%).

Preparation: Preparation of Form I comprises:

(1) combining Form II with an azeotropic solvent;

(2) submitting the obtained azeotropic mixture to azeotropic distillation to form Form I and

(3) optionally recovering Form I.

The solvent is preferably methyl ethyl ketone (MEK).

L20 ANSWER 5 OF 24 WPIDS (C) 2002 THOMSON DERWENT

AN 2001-374334 [39] WPIDS

DNC C2001-114315

TI Analyzing molecular events in the brain, especially hippocampal tissue involves hybridizing isolated brain mRNA to oligonucleotide array, clustering groups of genes and analyzing alterations of expression levels of genes.

DC B04 D16

IN CAO, Y; MODY, M; TSIEN, J Z

PA (AFFY-N) AFFYMETRIX INC; (UYPR-N) UNIV PRINCETON

CYC 93

PI WO 2001030973 A2 20010503 (200139)* EN 53p

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2001024701 A 20010508 (200149)

ADT WO 2001030973 A2 WO 2000-US41515 20001025; AU 2001024701 A AU 2001-24701 20001025

FDT AU 2001024701 A Based on WO 200130973

PRAI US 2000-227639P 20000824; US 1999-161337P 19991025

AB WO 200130973 A UPAB: 20010716
NOVELTY - Analyzing (M1) genome-wide molecular events occurring in brain tissue involves hybridizing isolated brain mRNA to an oligonucleotide array, clustering groups of genes together using self-organizing map analysis, and analyzing alterations of expression levels of genes.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a brain development related nucleic acid molecule (I) comprising a defined sequence;

(2) isolating (M1) protein sequences involves assembling a hybridization reaction mixture containing one or more of isolated nucleic acid molecules in single stranded form, and a test sample that comprises the corresponding protein coding sequence in a single-stranded form, under conditions enabling hybridization of the isolated nucleic acid molecule and the protein sequence, by forming a double stranded nucleic acid molecule, separating the double stranded molecule comprising the isolated nucleic acid and the protein coding sequence and cloning the protein coding sequence;

(3) an isolated protein (II) produced by expression of the protein coding sequences isolated by (M1);

(4) antibodies immunologically specific for (II);

(5) a recombinant DNA molecule comprising a protein coding sequence produced by (M1), operably linked to a vector for transforming cells;

(6) **screening** (M1) for candidate drugs which induce or inhibit expression of genes in the hippocampus involves contacting a hippocampal cell with a candidate drug for sufficient time for detectable expression of a gene and assaying for the amount of expression in the cell (II), or two or more of the following genes (III) e.g. **cyclin-dependent kinase** regulatory subunit 2, cyclin B2, cyclin G2, G1/S-specific cyclin D2, D-type G1 cyclin catalytic subunit (PSK-J3/ **CDK4**), cell division protein kinase 4(PSK-J3), D-type cyclin (CYL2), GADD45 (growth arrest and DNA damage induced protein), WW-domain binding protein-1, elongation factor-1- alpha , elongation factor-1- gamma , elongation factor-2 (EF-2), initiation factor 2 associated 67Kd glycoprotein, tubulin beta -1 chain, tubulin alpha -1, tubulin alpha -4, tubulin alpha -5, tubulin alpha -6, tubulin alpha -8, tubulin beta -3, tubulin beta -4 (class III), tubulin alpha -2, tubulin M- alpha -3, tubulin M- beta -5, CCT eta subunit (chaperonin containing TCP-1), CCT epsilon subunit (chaperonin containing TCP-1), CCT eta subunit (chaperonin containing TCP-1), CCT epsilon / theta subunit (chaperonin containing TCP-1), fatty acid synthase, Lipoprotein lipase precursor, squalene epoxidase, cell division control protein 4, transcription factor Sox-M, phosphofructokinase (PFK), pyruvate kinase, glucose-6-phosphate isomerase, fructose bisphosphate aldolase A, triose phosphate isomerase, sodium/potassium transporting ATPase beta -1 chain, sodium/potassium transporting ATPase alpha -2 chain, calcium-transporting ATPase sarcoplasmic reticulum type, and calcium-transporting ATPase endoplasmic reticulum type class 2. The expression of the genes in the cell is assayed before and after the cell has been contacted with the test substance, and in which the candidate drug is identified if it increases or decreases expression of one or more of the genes; and

(7) treating a disease involves administering to a diseased patient, (III) or a polypeptide which competes with the polypeptide encoded by one of the above genes for its ligand, substrate or receptor.

ACTIVITY - Cytostatic; neuroprotective.

MECHANISM OF ACTION - Gene therapy.

USE - (II) is useful for treating a disease in a patient which involves administering (II) or a polypeptide which competes with the polypeptide encoded by (III) for its ligand, substrate or receptor (claimed). The proteins encoded by the novel genes provide novel

biological targets for neuronal disorders associated with the aberrant expression of brain development-related nucleic acids. The novel genes are also useful as probes to determine the expression pattern of unknown cells or to identify a sample of tissue or cell as belonging to the appropriate developmental stage or organ source, to identify human homologues, as tools in the development of therapeutic drugs for treating neuronal degeneration diseases, nerve injuries, aging and cancer, as molecular expression markers, especially hippocampal tissue to confirm tissues of identifications made on the basis of morphological criteria, monitoring disease progression involving brain tissue and for monitoring the efficacy of certain drug treatments. Neuronal disorders can also be diagnosed by determining from a sample derived from a subject, an abnormally decreased or increased level of the novel genes on corresponding mRNA. The nucleic acid sequences are also useful as primers to amplify corresponding full length nucleic acids.

ADVANTAGE - The cluster method accurately reflects the potential underlying molecular and genetic programs during the hippocampal development.

Dwg.0/4

TECH UPTX: 20010716

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Gene: **Cyclin-dependent kinase** regulatory subunit 2, cyclin B2, cyclin G2, G1/S-specific cyclin D2, D-type G1 cyclin catalytic subunit (PSK-J3/**CDK4**), cell division protein kinase 4(PSK-J3), D-type cyclin (CYL2), GADD45 (growth arrest and DNA damage induced protein), oral tumor suppressor homolog (Doc-1), p53 cellular tumor antigen, DNA topoisomerase II, proliferating cell nuclear antigen, RNA polymerase I, 40 kD subunit, RNA helicase and RNA-dependent ATpase from DEAD box family, U2-snRNPb (pRNP11), U6-snRNA-associated protein, unwinding protein 1-, pre-mRNA splicing factor SRP75, myoblast cell surface antigen 24.1D5, histone H2A.X, replication-dependent histone H2A.1, H1 histone subtype H1(0), histone H2A.Z, J kappa RS-binding protein, transcription factor BTF3, neurogenin-2 (ngn2), myelin transcription factor 1, CAAT-box DNA binding protein subunit B (NF-YB), WW-domain binding protein-1, elongation factor-1-alpha, elongation factor-1-gamma, elongation factor-2 (EF-2), initiation factor 2 associated 67Kd glycoprotein, translational initiation factor 2 beta subunit (EIF-2), ubiquitin-conjugating enzyme E2, 60S ribosomal protein A52, ribosomal protein L5, ribosomal protein L8(RPL8), 60S ribosomal protein L9, ribosomal protein L12 (RPL12), 60S ribosomal protein L13A, ribosomal protein L18(RPL18), ribosomal protein L19, ribosomal protein L30, 60S ribosomal protein L23, 60S ribosomal protein L32, 60S ribosomal protein L34, 60S ribosomal protein L37, ribosomal protein S8, 40S ribosomal protein L24, ribosomal protein Ke-3, actin, cytoplasmic 1 (beta actin), actin-1, actin-3, cytoskeletal gamma actin, tubulin M-alpha-3, tubulin beta-1 chain, tubulin alpha-1, tubulin alpha-4, tubulin alpha-5, tubulin alpha-6, tubulin alpha-8, tubulin beta-3, tubulin beta-4 (class III), tubulin alpha-2, tubulin M-alpha-3, tubulin M-beta-5, CCT eta subunit (chaperonin containing TCP-1), CCT epsilon subunit (chaperonin containing TCP-1), CCT eta subunit (chaperonin containing TCP-1), CCT epsilon/theta subunit (chaperonin containing TCP-1), TCP-1 chaperonin cofactor A, valyl-tRNA synthetase, threonyl-tRNA synthetase, ubiquitin-conjugating enzyme (UbcM2), ubiquitin carboxyl-terminal hydrolase, ubiquitin-activating enzyme E1-X, cysteine protease, collagen alpha-1, type IV (col4a-1), fibronectin (FN), tenascin, gamma-actin, L1-like protein, neural cell adhesion molecule, (NCAM), neural cell adhesion molecule L1 (NCAM-L1), neurophilin, neural cadherin (N-cadherin), membrane-type matrix metalloproteinase 1, brain fatty acid-binding protein (B-FABP), fatty acid synthase, Lipoprotein lipase precursor, squalene epoxidase, Farnesyl pyrophosphate synthetase, keratinocyte lipid-binding protein, myelin gene expression factor (MEF-2), N-glycan alpha

2,8-sialyltransferase, clathrin, light chain B, synaptogamin I/65, UNC-18 homologue, vesicle associated membrane protein (VAMP2), synaptophysin (major synaptic vesicle protein P38), neuronal pentraxin 1, N-methyl-D-aspartate receptor-glutamate binding chain, neurogranin (protein kinase C substrate 7.5 kD), alpha-SNAP protein, calcium-activated potassium channel, potassium channel, beta-subunit, brain neurotensin receptor, acetylcholine receptor-interacting protein (AIP), fractalkine, cholecystokinin, brain derived neurotrophic factor (BDNF), glutamate receptor 1 (GluR1), glutamate receptor 2 (GluR2), SH3-containing protein (SH3P4), SH3P9, C-H-Ras, Ras-related protein RAB-3A, mitogen activated protein kinase (erk-1), receptor-type tyrosine kinase, focal adhesion kinase, calcineurin, phospholipase C beta 1, diglyceride kinase, RhoB, protein kinase C, cell division cycle homolog (CDC25), elongation factor(alpha-CMS1), growth factor-induced protein (zif/268), DNA-binding protein (Smbp-2), protooncogene DBL, transcriptional activator FE6J, cell division control protein 4, transcription factor Sox-M, phosphofructokinase (PFK), pyruvate kinase, glucose-6-phosphate isomerase, fructose bisphosphate aldolase A, triose phosphate isomerase, gamma enolase (2-phospho-D-glycerate hydrolyase), alpha- enolase (2-phospho-D-glycerate hydrolase), glycogen phosphorylase, glycerol kinase, NADH-ubiquinone oxidoreductase chain 49 kD subunit, NADH-ubiquinone oxidoreductase AGGG subunit precursor, cytochrome c oxidase subunit VIII precursor (Cox81), succinate dehydrogenase, malate dehydrogenase, lactate dehydrogenase-B, glycerophosphate dehydrogenase, antioxidant protein 2 (AOP2), ryanodine receptor type 2, vacuolar adenosine triphosphatase, subunit B, vacuolar adenosine triphosphatase, subunit E, voltage-dependent anion channel 1, sodium/potassium transporting ATPase beta-1 chain, sodium/potassium transporting ATPase alpha-2 chain, calcium-transporting ATPase sarcoplasmic reticulum type, Vacuolar ATP synthase subunit C, vacuolar ATP synthase subunit AC45, vacuolar ATP synthase 16 KD proteolipid subunit, and calcium-transporting ATPase endoplasmic reticulum type class 2.

Preferred Method: The brain mRNA employed in (M1) is an hippocampal mRNA.

Preferred Nucleic Acid: (I) comprises a sequence selected from the following accession numbers: having an accession number of TC14224, TC14254, TC14312, TC14325, TC14329, TC14435, TC14474, TC14629, TC14635, TC14704, TC14731, TC14735, TC14762, TC14763, TC14785, TC14788, TC14810, TC14823, TC14941, TC14972, TC14982, TC15012, TC15118, TC15133, TC15141, TC15204, TC15267, TC15448, TC15584, TC15665, TC15831, TC15974, TC16153, TC16205, TC16355, TC16494, TC16651, TC16708, TC17122, TC17275, TC17320, TC17874, TC17980, TC18222, TC18241, TC18400, TC18401, TC18687, TC18688, TC18708, TC18783, TC18804, TC18850, TC18869, TC18884, TC19058, TC19062, TC19069, TC19082, TC19105, TC19136, TC19211, TC19521, TC19732, TC19823, TC19926, TC19967, TC20099, TC20539, TC20803, TC21082, TC21205, TC21335, TC21412, TC21626, TC21685, TC21976, TC22202, TC22386, TC22448, TC22529, TC22542, TC22668, TC22669, TC22696, TC22785, TC23211, TC23244, TC23261, TC23542, TC23801, TC23956, TC24584, TC26547, TC26624, TC26682, TC27097, TC27333, TC27344, TC27510, TC27517, TC27528, TC27570, TC27571, TC27572, TC27573, TC27712, TC27850, TC27894, TC27963, TC28142, TC28255, TC28416, TC28417, TC28666, TC28824, TC28847, TC28859, TC28885, TC29042, TC29129, TC29216, TC29328, TC29385, TC29394, TC29445, TC29454, TC29479, TC29708, TC29810, TC30188, TC30208, TC30378, TC30379, TC30391, TC30530, TC30545, TC30555, TC30650, TC30755, TC30788, TC30805, TC30906, TC30918, TC30981, TC30987, TC31022, TC31051, TC31091, TC31128, TC31250, TC31334, TC31339, TC31349, TC31386, TC31671, TC31678, TC31686, TC31729, TC31755, TC31774, TC31783, TC31827, TC31864, TC31882, TC31917, TC31921, TC32043, TC32074, TC32106, TC32222, TC32250, TC32296, TC32304, TC32321, TC32325, TC32339, TC32438, TC32456, TC32559, TC32602, TC32713, TC32808, TC32829, TC32833, TC32980, TC33002, TC33009, TC33036, TC33177, TC33178, TC33179, TC33208, TC33209, TC33231, TC33232, TC33244, TC33290, TC33306, TC33377, TC33378,

TC33384, TC33396, TC33407, TC33529, TC33531, TC33738, TC33757, TC33765, TC33775, TC33788, TC33816, TC33823, TC33849, TC33852, TC33859, TC33866, TC33882, TC33985, TC34265, TC34289, TC34379, TC34965, TC34983, TC35017, TC35086, TC35131, TC35597, TC35648, TC35734, TC35822, TC35823, TC35874, TC35937, TC35974, TC36080, TC36082, TC36142, TC36344, TC36565, TC36683, TC36730, TC36740, TC36797, TC36816, TC36917, TC36970, TC37016, TC37019, TC37101, TC37186, TC37226, TC37230, TC37266, TC37268, TC37366, TC37388, TC37411, TC37468, TC37472, TC37670, TC37689, TC37720, TC37721, TC37793, TC37904, TC38039, TC38045, TC38052, TC38091, TC38092, TC38136, TC38142, TC38247, TC38281, TC38297, TC38377, TC38446, TC38523, TC38552, TC38590, TC38627, TC38806, TC38862, TC38867, TC39079, TC39101, TC39196, TC39214, TC39296, TC39303, TC39305, TC39334, TC39418, TC39420, TC39605, TC39644, TC39809, TC39826, TC39827, TC39868, TC39877, TC39895, TC39990, TC40025, TC40265, TC40450, TC40459, TC40494, TC40580, TC40603, TC40618, TC40687, TC40689, TC40704, TC40734, TC40780, TC40817, TC40833, TC40840, TC40879, TC40931, TC40975, TC41027, TC41069, TC41106, TC41175, TC41197, TC41200, TC41472, TC41499, TC41551, TC41561, TC41569, TC41588, TC41818, TC41859, TC41872, TC41992 or TC42517.

L20 ANSWER 6 OF 24 WPIDS (C) 2002 THOMSON DERWENT
AN 2001-335437 [35] WPIDS
CR 2001-308010 [23]
DNC C2001-103562
TI New 8H-pteridine-7-ones, tetrahydropteridin-7-ones, 5H,8H-pteridine-6,7 diones and pteridine-7-ureas, useful as kinase inhibitors for treating e.g. cancer and viral and fungal infections.
DC B02
IN DENNY, W A; DOBRUSIN, E M; KRAMER, J B; MC NAMARA, D J; REWCASTLE, G W; SHOWALTER, H D H; TOOGOOD, P L
PA (WARN) WARNER LAMBERT CO
CYC 85
PI WO 2001019825 A1 20010322 (200135)* EN 111p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AU BA BB BG BR BZ CA CN CR CU CZ DM DZ EE GD GE HR HU ID IL IN IS JP KP KR LC LK LR LT LV MA MG MK MN MX MZ NO NZ PL RO SG SI SK SL TR TT UA US UZ VN YU ZA
AU 2000056295 A 20010417 (200140)
ADT WO 2001019825 A1 WO 2000-US17037 20000621; AU 2000056295 A AU 2000-56295 20000621
FDT AU 2000056295 A Based on WO 200119825
PRAI US 1999-154095P 19990915
AB WO 200119825 A UPAB: 20010625
NOVELTY - 8H-Pteridine-7-ones, tetrahydropteridin-7-ones, 5H,8H-pteridine-6,7 diones and pteridine-7-ureas and their salts are new.
DETAILED DESCRIPTION - 8H-Pteridine-7-ones, tetrahydropteridin-7-ones, 5H,8H-pteridine-6,7 diones and pteridine-7-ureas of formula (I1), (I2'), (I3) and (I4') and their salts, esters, amides and prodrugs are new.
W = NH, S, SO, SO2;
R2 = 1-10C alkyl, 2-10C alkenyl, 2-10C alkynyl, 3-10C cycloalkyl, (CH2)n-aryl, COR4, (CH2)n-heteroaryl or (CH2)n-heterocyclyl (all optionally substituted by 1-5 of halo, amino, alkylamino, dialkylamino, alkoxy, aminoalkoxy, alkylaminoalkoxy, dialkylaminoalkoxy, phenyl (optionally substituted), phenoxy (optionally substituted), OH, thio, alkylthio, cyano, nitro, alkanoyl, aminoalkanoyl, alkylaminoalkanoyl, dialkylaminoalkanoyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, amino-3-7C cycloalkylcarbonyl, alkylamino-3-7C cycloalkylcarbonyl, dialkylamino-3-7C cycloalkylcarbonyl, COZ, CO2Z, SOZ, SO2Z, PO3Z, a carbocyclic group containing 3-7 ring members, 1 or 2 of

which may be O or N, and where the carbocyclic group may be substituted by 1-3 of halo, OH, alkyl, aminoalkyl, alkyl, dialkylaminoalkyl, CF3, alkoxy, amino, alkylamino, dialkylamino, alkanoylamino, COZ, CO2Z, SOZ, SO2Z, PO3Z, aryl, heteroaryl, (CH2)nmorpholino, (CH2)npiperazinyl, (CH2)npiperadinyl or (CH2)ntetrazolyl; or CF3;

R4, R6, R9, R6' = H, halo, lower alkyl, lower alkoxy, substituted alkyl, (CH2)n-alkenyl, (CH2)n-alkynyl, (CH2)n-cyano, amino, aminoalkoxy, phenoxy, OH, CF3, mono or dialkylamino, mono or dialkylaminoalkoxy, thiol, thioalkyl, nitrile, nitro, carboxylic acid, carboxylic acid esters, carboxamides, SO2Z, PO3Z, COZ, CO2Z, SOZ, aminoalkanoyl, aminocarbonyl, amino-3-7C cycloalkylcarbonyl or N-mono or N,N-dialkylaminocarbonyl; (CH2)naryl, (CH2)n-heteroaryl, arylalkyl or heteroarylalkyl, where aryl and heteroaryl are optionally substituted by up to 5 of halo, OH, lower alkyl or substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, lower alkoxy, amino, mono- or dialkylamino, CF3, thiol, thioalkyl, nitrile, nitro, carboxylic acid, carboxylic acid esters, carboxamides, SO3Z or PO3Z;

R8 = H, lower alkyl substituted alkyl, (CH2)n-alkenyl, substituted alkenyl, (CH2)n alkynyl, substituted alkynyl, or a (CH2)n-carbocyclic group containing 3-7 members, up to 2 of which may be O or N, and where the carbocyclic group is optionally substituted by 1-3 of halo, OH, lower alkyl, acetoxy, amino, COZ, CO2Z, SOZ, SO2Z, PO3Z, mono- or dialkylamino, aryl or heteroaryl; (CH2)n-aryl, (CH2)n-heteroaryl, arylalkyl or heteroarylakyl, where each aryl or heteroaryl is optionally substituted by up to 5 of halo, OH, lower alkyl substituted alkyl, lower alkoxy, amino, mono or dialkylamino, CF3, optionally substituted alkenyl, optionally substituted alkynyl, thiol, thioalkyl, nitrile, nitro, carboxylic acid, carboxylic acid esters, carboxamides, COZ, CO2Z, SOZ, SO2Z or PO3Z;
n = 0-6;

provided that R8 is other than H or 1-3C alkyl, when R2 = Me, Et or acetyl.

Z = H, OH, alkoxy, SOZ, lower alkyl, substituted alkyl, amino, alkylamino or dialkylamino; piperidinyl, morpholinyl or piperazinyl (all optionally substituted);

Q = H, lower alkyl or substituted alkyl;

R5, R7 = H, halo, amino, aminoalkyl, lower alkoxy, OH, phenoxy, thiol, thioalkyl, nitro, nitrile, optionally substituted phenyl, heteroaryl, CF3, mono or dialkylamino, mono- or dialkylaminoalkoxy, alkanoylamino, carbamoyl, amino-3-7C cycloalkylcarbonyl, N-mono or N,N-dialkylcarbamoyl, COZ, CO2Z, SOZ, SO2Z or PO3Z; lower alkyl optionally substituted by 1 or 2 of lower alkoxy, halo, amino, OH, mono- or dialkylamino, aryl or a carbocyclic group containing 3-7 members, up to 2 of which are O or N, where the carbocyclic group is optionally substituted by 1-3 of halo, OH, lower alkyl, lower alkoxy, amino, or mono- or dialkylamino; or a carbocyclic containing 3-7 members, up to 2 of which are O or N, where the carbocyclic group is optionally substituted by 1-3 of halo, OH, lower alkyl, CF3, lower alkoxy, amino, mono or dialkylamino, aryl, heteroaryl, morpholinoalkyl, piperazinylalkyl, piperadinylalkyl, tetrazolylalkyl, aminoalkyl or alkanoylamino;

R8' = as for R8 without the proviso.

ACTIVITY - Cytostatic; cardiant; arteriosclerotic; virucide; antifungal; antidiabetic; ophthalmological; nephrotropic; nootropic; neuroprotective; immunosuppressive; antipsoriatic; antirheumatic; antiarthritic; dermatological; antiinflammatory; antigout; vasotropic.

MECHANISM OF ACTION - Inhibitors of cyclin-dependent serine/threonine kinase, Wee 1 tyrosine kinase, and growth factor mediated tyrosine kinase enzymes. The **cyclin-dependent kinase** is especially cdc2, cdk2, **cdk4** or cdk6. The growth factor-mediated tyrosine kinase is platelet derived growth factor (PDGF) or fibroblast growth factor (FGF) (claimed).

8-Methyl-2-((4-(morpholin-4-yl)phenyl)amino)-6-phenyl-8H-pteridin-7-one (Ia) exhibited IC50 values of more than 50 micro M each for the inhibition of Wee 1 tyrosine kinase, C-src, FRGF and PDGF.

USE - For controlling proliferative disorders in a mammal selected from cancer, psoriasis, vascular smooth muscle proliferation associated with a disorder selected from atherosclerosis, postsurgical vascular stenosis and restenosis. For treating a mammal suffering from cardiovascular diseases including angiogenesis, viral infections including DNA viruses such as herpes and RNA viruses such as HIV; fungal infections; type 1 diabetes and diabetic neuropathy and retinopathy; multiple sclerosis; glomerulonephritis; neurodegenerative diseases including Alzheimer's disease; autoimmmune diseases such as rheumatoid arthritis, lupus, organ transplant rejection and host versus graft disease; gout; polycystic kidney disease; and inflammation including inflammatory bowel disease (all claimed). Also as research tools for studying the mechanism of action of the above kinases, both in vivo and in vitro.

Dwg.0/0

TECH UPTX: 20010625

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) may be prepared e.g. by cyclizing 2,4,5-triaminopyrimidine of formula (II) to the desired pteridine-7-one or 6,7-dione by reaction with the appropriate pyruvate or oxalate at elevated temperatures of 50-150 degreesC to give compounds of formula (I') and (I'') as shown below.

R1' = an oxalate or pyruvate ester forming group, e.g. 1-6C alkyl such as Et.

L20 ANSWER 7 OF 24 WPIDS (C) 2002 THOMSON DERWENT
AN 2001-235018 [24] WPIDS
DNC C2001-070400
TI Imidazo(1,2a)pyridine and pyrazolo(2,3a)pyridine derivatives useful as a medicament for the treatment of e.g. cancers, psoriasis and rheumatoid arthritis.
DC B02
IN BEATTIE, J F; BREAULT, G A; JEWSBURY, P J; THOMAS, A P
PA (ASTR) ASTRAZENECA AB; (ASTR) ASTRAZENECA UK LTD
CYC 93
PI WO 2001014375 A1 20010301 (200124)* EN 81p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000065833 A 20010319 (200136)
ADT WO 2001014375 A1 WO 2000-GB3139 20000815; AU 2000065833 A AU 2000-65833 20000815
FDT AU 2000065833 A Based on WO 200114375
PRAI GB 1999-19778 19990821
AB WO 200114375 A UPAB: 20010502

NOVELTY - Imidazo(1,2a)pyridine and pyrazolo(2,3a)pyridine derivatives (I) their salts or in vivo hydrolyzable ester are new.

DETAILED DESCRIPTION - Imidazo(1,2a)pyridine and pyrazolo(2,3a)pyridine derivatives, their salts or in vivo hydrolyzable ester of formula (I) are new:

Ring A = imidazo(1,2a)pyrid-3-yl or pyrazolo(2,3a)pyrid-3-yl;

R2 is attached to a ring C = halo, nitro, cyano, OH, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulfamoyl, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 1-6C alkoxy, 1-6C alkanoyl, 1-6C alkanoyloxy, N-(1-6C alkyl)amino, N,N-(1-6C alkyl)2amino, 1-6C alkanoylamino, N-(1-6C alkyl)carbamoyl, N,N-(1-6C alkyl)2carbamoyl, 1-6C

alkylS(O)a, 1-6C alkoxycarbonyl, N-(1-6C alkyl)sulfamoyl, N,N-(1-6C alkyl)2sulfamoyl, phenyl, heterocyclic group, phenylthio or (heterocyclic group)thio;

where any 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, phenyl or heterocyclic group may be optionally substituted on carbon by one or more G; and where if heterocyclic group contains an NH moiety that nitrogen may be optionally substituted by a group selected from Q;

a = 0-2;

m = 0-5;

R1 = halo, nitro, cyano, OH, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulfamoyl, 1-3C alkyl, 2-3C alkenyl, 2-3C alkynyl, 1-3C alkoxy, 1-3C alkanoyl, N-(1-3C alkyl)amino, N,N-(1-2C alkyl)2amino, 1-3C alkanoylamino, N-(1-3C alkyl)carbamoyl, N,N-(1-2C alkyl)2carbamoyl, 1-3C alkylS(O)a, N-(1-3C alkyl)sulfamoyl or N,N-(1-3C alkyl)2sulfamoyl,

where any 1-2C alkyl, 1-3C alkyl, 2-3C alkenyl, 2-3C alkynyl, phenyl or heterocyclic group may be optionally substituted on carbon by one or more J;

n = 0-2;

Ring B = phenyl or phenyl fused to a 5-7C cycloalkyl;

R3 = halo, nitro, cyano, OH, amino, carboxy, carbamoyl, mercapto, sulfamoyl, 2-6C alkenyl or 2-6C alkynyl;

p = 0-4;

R4 = A-E-;

A = 1-6 alkyl, phenyl, a heterocyclic group, 3-8C cycloalkyl, phenyl1-6C alkyl, (heterocyclic group)1-6C alkyl, or 3-8C cycloalkyl1-6C cycloalkyl; all optionally substituted on carbon by one or more D; and if heterocyclic group contains an NH moiety that nitrogen may be optionally substituted by a group selected from R;

E = direct bond, O, CO, OCO, COO, N(Ra)CO, CON(Ra), N(Ra), S(O)r, SO2N(Ra) or N(Ra)SO2;

Ra = H or 1-6C alkyl optionally substituted by one or more D;

r = 0-2;

D = oxo, halo, nitro, cyano, OH, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulfamoyl, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 1-6C alkoxy, 1-6C alkanoyl, 1-6C alkanoyloxy, N-(1-6C alkyl)amino, N,N-(1-6C alkyl)2amino, 1-6C alkanoylamino, N-(1-6C alkyl)carbamoyl, N,N-(1-6C alkyl)2carbamoyl, 1-6C alkylS(O)a, 1-6C alkoxycarbonyl, 1-6C alkoxycarbonylamino, benzyloxycarbonylamino, N-(1-6C alkyl)sulfamoyl or N,N-(1-6C alkyl)2sulfamoyl;

where any 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl,or phenyl may be optionally substituted on carbon by one or more K;

q = 0-2;

p+q at most 5;

G, J, K = halo, nitro, cyano, OH, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylamino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulfamoyl, N-ethylsulfamoyl, N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl or N-methyl-N-ethylsulfamoyl; and

Q, R = 1-4C alkyl, 1-4C alkanoyl, 1-4C alkylsulfonyl, 1-4C alkoxycarbonyl, carbamoyl, N-(1-4C alkyl)carbamoyl, N,N-(1-4C alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl or phenylsulfonyl.

ACTIVITY - **Anticancer**; Antipsoriatic; Antirheumatic; Antiarthritic; Cytostatic; Antiarteriosclerotic; Anti-HIV; Vasotropic; Immunosuppressive; Antiinflammatory; Osteopathic; Ophthalmological.

MECHANISM OF ACTION - **Cyclin-dependent**

kinases (CDK2, **CDK4** and/or CDK6) inhibitors. Typical IC50 values for (I) when tested in the Sulforhodamine B (SRB) assay ranged from 1 mM to 1nM.

USE - (I) are used in a medicament for the treatment of cancers (solid tumors and leukemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation. (all claimed)

Dwg.0/0

TECH UPTX: 20010502

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: compounds of formula (I) are prepared by

(a) reacting a pyrimidine of formula (II) with an amine of formula (III);
(b) reacting a pyrimidine of formula (IV) with a compound of formula (V);
(c) reacting a compound of formula (VI) with a compound of formula (VII);

and thereafter if necessary:

(i) converting a compound of formula (I) into another compound of formula (I);
(ii) removing any protecting groups; and
(iii) forming a salt or in vivo hydrolyzable ester.

L = displaceable group;
one of M and Q = displaceable group X and the other is a metallic reagent Y;
R5 = 1-6C alkyl; and
R6 = H or R1.

L20 ANSWER 8 OF 24 WPIDS (C) 2002 THOMSON DERWENT
AN 2001-168526 [17] WPIDS
DNC C2001-050347
TI New biarylurea derivatives are **cyclin dependent kinase** inhibitors useful as **antitumor** agents.
DC B05
IN HAYAMA, T; HAYASHI, K; HONMA, M; TAKAHASHI, I
PA (BANY) BANYU PHARM CO LTD
CYC 92
PI WO 2001007411 A1 20010201 (200117)* JA 460p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AU AZ BA BB BG BR BY CA CN CR CU CZ DM DZ EE GD GE HR HU ID IL IN IS KG KR KZ LC LK LR LT LV MA MD MG MK MN MX MZ NO NZ PL RO RU SG SI SK TJ TM TR TT UA US UZ VN YU ZA
AU 2000063149 A 20010213 (200128)
JP 2001106673 A 20010417 (200128) 239p
ADT WO 2001007411 A1 WO 2000-JP4991 20000726; AU 2000063149 A AU 2000-63149 20000726; JP 2001106673 A JP 2000-274175 20000726
FDT AU 2000063149 A Based on WO 200107411
PRAI JP 1999-211384 19990726
AB WO 200107411 A UPAB: 20010328

NOVELTY - Biarylurea derivatives (I) are new.

DETAILED DESCRIPTION - Biarylurea derivatives of formula (I) and their salts are new.

Ar = optionally substituted nitrogenous heterocyclic aromatic;
R1 = H, Y3W2Y4Rs or lower alkyl (optionally substituted by Y3W2Y4Rs);
Rs = H or optionally substituted aliphatic heterocyclyl;
W2 = a bond, O, S, SO2NRt, SO2NRt, NRtSO2NRu, NRtSO2, CH(ORt), CONRt, NRtCO, NRtCONRu, NRtCOO, NRtCSO, NRtCOS, CRv=CRr, CC, CO, CS, OCO, OCONRt, OCSNRt, SCO, SCONRt or COO;
Rr, Rt, Ru, Rv = H or optionally substituted lower alkyl, aryl or

aralkyl;
Y3, Y4 = a bond or optionally substituted lower alkylene;
X, Z = C, CH or N;
Y = CO, SO, SO or SO2;
R2, R3 = H, OH, lower alkyl, lower alkoxy or Y3W2Y4Rs, or
R1 + R2 = a bond, or
ZR2R3 = CO, or
XR1 or R2 + R3 = a ring;
R4, R5 = H, halo, OH, amino, Y3W2Y4Rs or lower alkyl, aryl or aralkyl (all optionally substituted by Y3W2Y4Rs).
N.B. Definitions in the specification are extremely long and substituents and provisos are given.
An INDEPENDENT CLAIM is included for the preparation of (I).
ACTIVITY - Cytostatic.
In cell culture assays a compound of formula (Ia) had IC50 values for HCT116 and MKN-1 cell of 0.013 and 0.10 mu M, respectively, compared to 0.15 and 0.87 mu M respectively for (+/-)flavopiridol.
MECHANISM OF ACTION - Cyclic dependent kinase (**CDK**)-4 inhibitor; CDK-6 inhibitor.
USE - Used as **tumor** cell proliferation **inhibitors** useful as **antitumor** agents.
Dwg.0/0

TECH UPTX: 20010328
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Preparation of (I) comprises reacting a bicyclic compound of formula (V) with H2NAr0 and optionally deprotecting or further converting any groups.
R10, R20, R30, R40, R50, Ar0 = optionally protected R1-R5 or Ar, respectively, or groups convertible to R1-R5 or Ar, respectively.

L20 ANSWER 9 OF 24 WPIDS (C) 2002 THOMSON DERWENT
AN 2001-159879 [16] WPIDS
DNC C2001-047631
TI Composition comprising a human **cyclin-dependent kinase** (Cdk)/cyclin complex which serves as a substrate for Cdc25 phosphatase, useful for identifying Cdc25 phosphatase inhibitors which can be used to treat cancers and leukemia.
DC B04 D16
IN ECKSTEIN, J; EPSTEIN, D; RUDOLPH, J
PA (BADI) BASF BIORESEARCH CORP; (GPCB-N) GPC BIOTECH INC
CYC 93
PI WO 2001009373 A2 20010208 (200116)* EN 58p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000063945 A 20010219 (200129)
ADT WO 2001009373 A2 WO 2000-US20936 20000731; AU 2000063945 A AU 2000-63945 20000731
FDT AU 2000063945 A Based on WO 200109373
PRAI US 1999-364715 19990730
AB WO 200109373 A UPAB: 20010323
NOVELTY - A composition comprising a **cyclin-dependent kinase** (Cdk)/cyclin complex composed of human Cdk and cyclin proteins or their portions sufficient to form the complex and serve as a substrate for the Cdc25 phosphatase, is new.
DETAILED DESCRIPTION - A composition comprising a **cyclin-dependent kinase** (Cdk)/cyclin complex composed of human Cdk and cyclin proteins or their portions sufficient to form the complex

and serve as a substrate for the Cdc25 phosphatase, is new.

The Cdk/cyclin complex is homogenous with respect to the sequence of the Cdk and cyclin proteins, having a defined phosphorylation state. The composition substantially lacks other proteins that bind the cdk, cyclin or Cdk/cyclin complex.

INDEPENDENT CLAIMS are included for the following:

(1) a method (M1) of identifying an inhibitor of human Cdc25 phosphatase activity, comprising:

(a) combining a Cdc25 phosphatase, phosphorylated complexes of mammalian Cdk and cyclin polypeptides (Cdk/cyclin complex), and a test compound, where the Cdc25 phosphatase will dephosphorylate the phosphorylated Cdk/cyclin complex in the absence of a Cdc25 phosphatase inhibitor and the reaction mixture is defined with respect to phosphorylation of the Cdk/cyclin complex, or is substantially free of Cdk/cyclin associated proteins, or both; and

(b) detecting T14 and/or Y15 dephosphorylation of the phosphorylated Cdk/cyclin complex, where the test compound is an inhibitor of the Cdc25 phosphatase if it decreases the ability of the Cdc25 phosphatase to dephosphorylate the phosphorylated Cdk/cyclin complex; and

(2) a method (M2) of identifying an inhibitor of human Cdc25 phosphatase activity, comprising:

(a) combining in a reaction mixture, a Cdc25 phosphatase, phosphorylated complexes of mammalian Cdk and cyclin polypeptides (Cdk/cyclin complex), and a test compound, where the Cdc25 phosphatase binds to the phosphorylated Cdk/cyclin complex in the absence of Cdc25 phosphatase inhibitor and the reaction mixture is defined with respect to phosphorylation of the Cdk/cyclin complex, or is substantially free of Cdk/cyclin associated proteins, or both; and

(b) detecting the formation of a complex between the Cdk/cyclin complex and the Cdc25 phosphatase, where the test compound is a Cdc25 phosphatase inhibitor if it decreases the ability of the Cdc25 phosphatase to bind the phosphorylated Cdk/cyclin complex.

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - Cdc25 inhibitor.

No relevant biological data given.

USE - The composition comprises a natural substrate for human Cdc25, which can be used for the direct measurement of Cdc25 activity in a quantifiable and reproducible manner. The inhibitors may be used to discriminate between the reactions of each phase of T14 or Y15 dephosphorylations. Cdc25 inhibitors are useful for modulating cell growth, differentiation or death, for treating diseases characterized by abnormal cell growth, e.g., hyperproliferative or hypoproliferative diseases, neoplastic and hyperplastic diseases, cancers, leukemia, fibroproliferative disorders, solid tumors, sarcomas and carcinomas (such as lung, colon, prostate, breast, ovary or esophagus cancer, melanoma, seminoma, and squamous adenocarcinoma), Hodgkin's lymphoma, or Waldestroem's macroglobulemia. These may also be used to inhibit differentiation of specific cells or the progression of pre-neoplastic lesions into a neoplastic lesion.

Dwg.0/3

TECH UPTX: 20010323

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: In M1, dephosphorylation of the phosphorylated Cdk/cyclin complex is determined by detecting the release of free inorganic phosphate (31P, 32P or 33P). The test compound is a peptide, a nucleic acid, a carbohydrate, a small organic molecule, or natural product extract or their fractions. The Cdk/cyclin complex is composed of human Cdk and cyclin polypeptides. The Cdk/cyclin complex is preferably a Cdk2/CycA complex, where Thr-161 of the Cdk protein is phosphorylated. The Cdk is phosphorylated by a Myt1 kinase derived from Xenopus, starfish, yeast, or Drosophila. The Cdk may

also be phosphorylated by a Wee1 kinase from Xenopus, used to phosphorylate the Cdk2/CycA complex. Wee1 kinase is derived from Xenopus, starfish, yeast, or Drosophila. The Cdk/cyclin complex includes less than 25% (w/v protein) of p13suc1, INK4 or WAF1/Cip1 proteins. It is further comprised of truncated or fusion protein forms of Cdk and cyclin proteins. The complex may be selected from Cdc2-/CycB, Cdk2/CycE, **Cdk4** /CycD, or Cdk6/CycD, or their fragments. The method further comprises formulating a pharmaceutical composition comprising one or more of the compounds or their derivatives identified as inhibitors of Cdc25 phosphatase.

In M2, the Cdc25 phosphatase is a catalytically inactive mutant that retains the ability to bind to the phosphorylated Cdk/cyclin complex.

Preferred Composition: At least 10% of the Cdk/cyclin complex in the composition are phosphorylated complexes, and at least 75% of the phosphorylated Cdk/cyclin complexes are bis-phosphorylated. The cdk consists of cdc2, cdk2, **cdk4**, or cdk6, and cyclin is selected from cyclin A, cyclin B, cyclin C, cyclin D or cyclin E. The complexes in the composition may consist of cdk2/cyclin A, **Cdk4**/cyclin A, cdk6/cyclin A, cdc2/cyclin A, cdk2/cyclin B, cdk2/cyclin E, or cdk2/cyclin B complexes. Thr-161 of the Cdk is phosphorylated.

L20 ANSWER 10 OF 24 WPIDS (C) 2002 THOMSON DERWENT
AN 2001-093033 [11] WPIDS
DNC C2001-027682
TI Linear DNA construct for neuron-specific expression, useful e.g. for gene therapy of neurodegenerative diseases, contains eukaryotic tumor suppressor gene.
DC B04 D16
IN ARENDT, T
PA (UYLE) UNIV LEIPZIG
CYC 1
PI DE 19936034 C1 20010125 (200111)* 5p
ADT DE 19936034 C1 DE 1999-19936034 19990730
PRAI DE 1999-19936034 19990730
AB DE 19936034 C UPAB: 20010224

NOVELTY - Recombinant, neuron-specifically activated, transcribable, linear DNA construct (A) comprises:

(i) a downstream transcribable eukaryotic tumor suppressor gene (II);

(ii) a neuron-specific DNA control element (I) to initiate transcription of (II); and

(iii) a reporter gene (III) downstream of (II).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a method for identifying DNA constructs that can inhibit cell death caused by neurodegeneration; and

(2) neuronal cells that contain (A).

ACTIVITY - Cytoprotective; Nootropic; neuroprotective; antiparkinsonian; immunosuppressive; antimicrobial; cardiant.

MECHANISM OF ACTION - Inhibition of cell-cycle activation by expressing a tumor suppressor gene, specific one encoding an inhibitor of the **cyclin-dependent kinase cdk4** which regulates the G0-G1 transition. Blocking of the cell cycle at this early stage results in re-differentiation of cells.

USE - (A) are used to examine agents for neuron-specific activity and to reduce damage to neuronal cells, specifically to protect against neurodegenerative diseases (e.g. Alzheimer's or Parkinson's diseases, amyotrophic lateral sclerosis, developmental disorders and infectious or autoimmune diseases) and to reduce the effects of ischemic and traumatic injuries.

Dwg.0/0

TECH UPTX: 20010224
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Construct: (I) is a synapsin I promoter; (II) encodes a cell-cycle inhibitor, particularly the p16 INK4 gene (encoding an inhibitor of the **cyclin-dependent kinase cdk4**), and (III) encodes beta-galactosidase.
Preferred Method: In method (1), (A) is introduced into neuronal cells using a modified viral vector (particularly lentiviral) so that (II) is expressed specifically and constitutively in neuronal cells. Expression of (II) is confirmed by expression of the product of (III).
Preparation: A lentiviral vector containing components (I)-(III) is assembled conventionally, then used to transfect neuronal cells so that after transfection, the construct is integrated stably into the genome. The transformed cells are then used for in vitro **screening** to identify constructs that are neuroprotective. Alternatively, the vector is used to generate transgenic animals for **screening**, e.g. by direct, stereotactic injection into the brain. The animal is then treated with a compound suspected of causing neurodegeneration and the degree of neuronal damage determined and compared with that in a control animal.

L20 ANSWER 11 OF 24 WPIDS (C) 2002 THOMSON DERWENT
AN 2000-181145 [16] WPIDS
DNC C2000-056517
TI Nucleic acid encoding recombinant human **cyclin-dependent kinase** binding protein (cdc37), used for regulating cell proliferation and differentiation, such as for treating cancer.
DC B04 D16
IN DRAETTA, G; GYURIS, J; LAMPHERE, L
PA (MITO-N) MITOTIX INC
CYC 1
PI US 6015692 A 20000118 (200016)* 32p
ADT US 6015692 A CIP of US 1994-253155 19940602, CIP of US 1995-466679 19950606, Cont of US 1996-625209 19960401, US 1997-853733 19970509
FDT US 6015692 A CIP of US 5691147, Cont of US 5756671
PRAI US 1996-625209 19960401; US 1994-253155 19940602; US 1995-466679 19950606; US 1997-853733 19970509
AB US 6015692 A UPAB: 20000330
NOVELTY - Pure nucleic acid (I) encoding a recombinant polypeptide (II) having a cdc37 sequence at least 80% identical with a 378 amino acid (aa) sequence (A), given in the specification, or its fragments, that bind specifically to at least one of **cyclin-dependent kinase** (CDK) and extracellular signal-regulated kinase (erk).
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(a) expression vector, replicable in eukaryotic and/or prokaryotic cells, comprising (I);
(b) host cell transfected with this vector and able to express (II);
(c) recombinant production of (II) by culturing cells of (b);
(d) composition comprising a purified oligonucleotide (ON) containing a region that hybridizes under stringent conditions with at least 50 consecutive nucleotides (nt) of the sense or antisense strands of a sequence (B) of 1599 bp (base pairs) (given in the specification), or its natural mutants;
(e) recombinant transfer system comprising gene construct that includes (B), operably linked to a transcriptional regulator and a gene delivery component; and
(f) test kit for detecting cells that contain a cdc37 mRNA transcript comprising the composition of (d).
ACTIVITY - **Antitumor**; growth regulatory; antipsoriatic; antiproliferative; anti-atherosclerotic; anti-inflammatory; antifungal.
No biological data.

MECHANISM OF ACTION - (II) binds to (and modulates) CDK/erk (possibly also p53), so regulates progress through the cell cycle and thus cell growth, differentiation and survival.

USE - (I) is useful:

(i) for producing recombinant (II);

(ii) as source of probes and primers for identifying transformed cells, measuring levels of cdc37-encoding nucleic acid and for detecting mutations or deletions in cdc37 genes (for diagnosis of cell proliferative disease or susceptibility);

(iii) in gene therapy, e.g. to promote regeneration of liver or lung tissue;

(iv) as antisense therapeutics, for treating cancer, leukemia, psoriasis, bone disease, fibroproliferation, atherosclerosis, chronic inflammation etc.; and

(v) for producing transgenic animals that express heterologous cdc37 or have an endogenous cdc37 gene deleted.

(II), or its fragments, are useful:

(i) for modulating growth, differentiation and survival of cells, including tumor cells;

(ii) as agonists or antagonists of wild-type cdc37;

(iii) as immunogens for raising specific antibodies (Ab); and

(iv) for **screening** for agents, potential antimycotics, that act on yeast CDC2/Cdc37 complexes but not on corresponding mammalian complexes.

Antagonists that inhibit interaction of cdc37 with other proteins, e.g. peptidomimetics or mutant forms of cdc37, are used to modulate cell proliferation and/or differentiation. Antibodies are used to **screen** cDNA expression libraries and as reagents for determination of cdc37 levels in tissues, e.g. for diagnosing cancer.

Dwg.0/1

TECH UPTX: 20000330

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred nucleic acid: (I) preferably hybridizes under stringent conditions to at least 60, preferably 120, nt of (B). It may also include a transcriptional regulatory sequence (for use as expression vector). ON preferably binds to at least 80 consecutive nt of (B), and may also include a detectable label or at least one non-hydrolyzable bond between adjacent nucleotide subunits.

Preferred protein: (II) binds to erk-1 or -2, or to a G1-phase CDK, particularly **CDK4**, optionally also to p53 protein. It modulates at least one of cell proliferation, differentiation and survival; particularly it stimulates or antagonizes activation of kinase activity of CDK. (II) is at least 90% identical with, or 95% homologous with, (A) and may be fused to an unrelated protein sequence, e.g. a detectable label, a matrix-binding domain (for immobilization) or an enzyme.

Preferred system: In the transfection system of (e), the delivery component is preferably a recombinant viral particle, liposome or polycationic nucleic acid binding agent.

Preparation: (I) was identified in an interaction trap assay (in yeast) based on:

(i) fusion protein comprising the LexA DNA-binding domain;

(ii) reporter gene in which the regulatory elements depend on binding to LexA; and

(iii) proteins encoded by an expression library.

Plasmid DNA was recovered from clones that showed galactose-dependent growth on leucine-deficient medium and galactose-dependent blue color on X-gal medium. One clone expressing cdc37 was identified; it can be expressed in any usual vector/host system, optionally as a fusion protein.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Fragments of (I) and (II) may also be prepared by conventional chemical synthesis.

L20 ANSWER 12 OF 24 WPIDS (C) 2002 THOMSON DERWENT
AN 2000-171024 [15] WPIDS
DNC C2000-053160
TI Early diagnosis of carcinoma or precarcinoma, especially of the cervix, by detecting overexpression of a cell-cycle regulatory protein.
DC B04 D16
IN VON KNEBEL DOEBERITZ, M; VON KNEBEL, M; SPITKOVSKY, D; VON KNEBEL, D M
PA (DOEB-I) DOEBERITZ M V K; (DEKR-N) DEUT KREBSFORSCHUNGSZENTRUM; (DOEB-I) VON KNEBEL DOEBERITZ M; (UYDO-N) UNIV DOEBERITZ CHIRURGISCHE MOLEKULARE; (DOEB-N) DOEBERITZ CHIRURGISCHE UNIVERSITAETSKLIN; (VKNE-I) VON KNEBEL M; (VKNE-N) VON KNEBEL DOEBERITZ CHIRURGISCHE UNIV; (VKNE-I) VON KNEBEL D M
CYC 85
PI WO 2000001845 A2 20000113 (200015)* DE 13p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
DE 19829473 A1 20000113 (200015)
AU 9958487 A 20000124 (200027)
DE 19829473 C2 20000810 (200039)
EP 1092155 A2 20010418 (200123) DE
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
NO 2000006681 A 20010226 (200123)
BR 9912227 A 20010424 (200128)
CZ 2000004922 A3 20010711 (200147)
SK 2000002031 A3 20011008 (200163)
CN 1307681 A 20010808 (200173)
HU 2001002744 A2 20011128 (200209)
KR 2001074632 A 20010804 (200210)
ADT WO 2000001845 A2 WO 1999-DE2094 19990701; DE 19829473 A1 DE 1998-19829473 19980701; AU 9958487 A AU 1999-58487 19990701; DE 19829473 C2 DE 1998-19829473 19980701; EP 1092155 A2 EP 1999-945931 19990701, WO 1999-DE2094 19990701; NO 2000006681 A WO 1999-DE2094 19990701, NO 2000-6681 20001228; BR 9912227 A BR 1999-12227 19990701, WO 1999-DE2094 19990701; CZ 2000004922 A3 WO 1999-DE2094 19990701, CZ 2000-4922 19990701; SK 2000002031 A3 WO 1999-DE2094 19990701, SK 2000-2031 19990701; CN 1307681 A CN 1999-807911 19990701; HU 2001002744 A2 WO 1999-DE2094 19990701, HU 2001-2744 19990701; KR 2001074632 A KR 2001-700026 20010102
FDT AU 9958487 A Based on WO 200001845; EP 1092155 A2 Based on WO 200001845; BR 9912227 A Based on WO 200001845; CZ 2000004922 A3 Based on WO 200001845; SK 2000002031 A3 Based on WO 200001845; HU 2001002744 A2 Based on WO 200001845
PRAI DE 1998-19829473 19980701
AB WO 200001845 A UPAB: 20020215
NOVELTY - Early diagnosis of carcinoma, or its precursor, comprises determining overexpression of a cell-cycle regulatory protein (I) in a body sample.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a kit comprising a reagent (II) for detecting (I), conventional auxiliaries (buffer, carrier, marker etc.) and optionally an agent for performing a control reaction.

USE - The method is used to diagnose carcinoma, especially of the cervix uteri, or its preliminary stages, e.g. cervical intraepithelial neoplasia or carcinoma in situ.

ADVANTAGE - The method is simple and quick and provides an early and reliable diagnosis, able to differentiate between carcinoma and benign

inflammation or metaplastic alterations. It does not involve a subjective assessment (contrast the standard Pap test) and is suitable for mass **screening**, e.g. in Third World countries. The degree of overexpression of (I) is correlated with the extent of cellular dysplasia. Dwg.0/2

TECH UPTX: 20000323

TECHNOLOGY FOCUS - BIOLOGY - Preferred process: The carcinoma is one that affects the upper respiratory tract or the anogenital region, particularly cervical carcinoma. The test sample is blood, a smear, sputum, urine, feces, liquor, bile, bone marrow, gastrointestinal secretion, organ punctate, biopsy and/or lymph, and overexpression is detected at nucleic acid or protein levels. In the kits, (II) is an antibody directed against (I), a nucleic acid, or its fragment, that encodes (I), (I), (II) or their fragments or a cell preparation.

Preferred proteins: (I) is a cyclin; a **cyclin-dependent kinase** (cdk), particularly **cdk4** or 6; or an inhibitor of cdk, particularly p14, p15, p16, p18, p19, p21 or p27.

L20 ANSWER 13 OF 24 WPIDS (C) 2002 THOMSON DERWENT
AN 2000-147033 [13] WPIDS
DNC C2000-045948
TI New use of indigoid bisindole derivatives for treating cancer, psoriasis, neurodegenerative disorders, glomerulonephritis.
DC B02
IN EISENBRAND, G; HOESSL, R; MARKO, D; MEIJER, L; TANG, W; HOESSEL, R; MEIER, L
PA (CNRS) CNRS CENT NAT RECH SCI FRANCE INNOVATION; (EISE-I) EISENBRAND G; (CNRS) CNRS CENT NAT RECH SCI; (CNRS) CENT NAT RECH SCI
CYC 80
PI WO 9962503 A2 19991209 (200013)* EN 25p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US
EP 966963 A1 19991229 (200013) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
AU 9943687 A 19991220 (200021)
NO 2000006027 A 20010122 (200112)
BR 9910810 A 20010213 (200114)
EP 1079826 A2 20010307 (200114) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
HU 2001002240 A2 20011128 (200209)
KR 2001078722 A 20010821 (200212)
ADT WO 9962503 A2 WO 1999-EP3625 19990526; EP 966963 A1 EP 1998-109845 19980529; AU 9943687 A AU 1999-43687 19990526; NO 2000006027 A WO 1999-EP3625 19990526, NO 2000-6027 20001128; BR 9910810 A BR 1999-10810 19990526, WO 1999-EP3625 19990526; EP 1079826 A2 EP 1999-926420 19990526, WO 1999-EP3625 19990526; HU 2001002240 A2 WO 1999-EP3625 19990526, HU 2001-2240 19990526; KR 2001078722 A KR 2000-713499 20001129
FDT AU 9943687 A Based on WO 9962503; BR 9910810 A Based on WO 9962503; EP 1079826 A2 Based on WO 9962503; HU 2001002240 A2 Based on WO 9962503
PRAI EP 1999-105693 19990319; EP 1998-109845 19980529
AB WO 9962503 A UPAB: 20000313
NOVELTY - Use of indigoid bisindole derivatives for the manufacture of a medicament for inhibiting **cyclin dependent kinases**.
ACTIVITY - **Anticancer**; antipsoriatic; vasotropic;

nephrotropic; nootropic; neuroprotective; anti-HIV. Indigo naturalis have hemostatic, antipyretic, antiinflammatory, sedative, antileukemic activities. No tests for determining the above mentioned activities are described in the source material.

MECHANISM OF ACTION - (I), (II) and (III) inhibit **cyclin dependent kinases** with high selectivity, particularly CDK1, CDK2, **CDK4** or CDK5 (claimed), more particularly ATP:Proteinphosphotransferase P34-cdc2 (CDK1). Indirubine-3-monoxime (Ia) was tested for inhibition of histone H1 phosphorylation, as a measure for CDK1/cyclin B activity after 24 hours incubation of MCF-7 mammary carcinoma cells. The content of cyclin B complex was significantly reduced. Cells arrested by serium deprivation after treatment for 24 hours with (Ia) in serum containing medium exhibited an arrest in G1-phase of cell cycle at lower micromolar concentration of (Ia). In concentration 1-5 mu M, an additional arrest at G2/M-phase at cell cycle became apparent. Cells arrested in G2/m by Nocodazole treatment after release of the block exhibited an increase of G2/M arrested cells on treatment with (Ia), resulting in a massive accumulation of cells in G2/M. Concomitantly with the observed intracellular effects, growth inhibition was induced in the same concentration range, resulting in an IC50 value of 3.3 plus or minus 0.7 mu M after 3 days incubation, induction of apoptotic cell death was observed. IC50 values of (Ia) was CDK1/cyclin B (0.180 mu M), CDK2/cyclin A (0.440 mu M), CDK2/cyclin E (0.250 mu M), CDK5/P35 (0.100 mu M) and value of **CDK4**/cyclin D1 inhibition was not determined.

Among the tested compounds (inhibitors) indirubine-5-sulfonic acid showed the best IC50 value of 0.055 mu M for CDK1/cyclin B, 0.035 mu M for CDK2/cyclin A, 0.150 mu M CDK2/cyclin E, 0.300 mu M for **CDK4** /cyclin D1 and 0.065 mu M for CDK5/P35.

USE - In analytical biochemistry especially for the study of cell cycle effects, for treating diseases connected to loss of proliferation control without any restriction to these potential areas of application, for treating cancers, psoriasis, cardiovascular diseases (stenosis, restenosis), infectious diseases (unicellular parasites like trypanosoma, toxoplasma, plasmodium etc.), fungi, etc. nephrology (glomerulonephritis), neurogenerative disorders like Alzheimer's diseases, viral infections like cytomegalovirus and HIV. Indirubine (from indigo naturalis) is also used for treating bacterial and viral infections and also as dyes.

ADVANTAGE - (I) has high selectivity and high efficiency for inhibition in comparison to other inhibitors like staurosporine, butyrolactone-1, flavopiridol, 9-hydroxyellipticin, olomoucine, roscovitine, isopentyladeine and some peptides.

Dwg.0/1

TECH UPTX: 20000313

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Inhibitor: The indigoid inhibitor compound is indigo, isoindigo or indirubine derivatives.

Preferred Compound: Indirubine derivative have the general formula (I), (II), and (III), where:

R1, R6 = H, halo, OH, CH2OH, (1-18C) alkyl, alkoxy or methylene alkoxy, 3-7C cycloalkyl, (aryl, aralkyl or aryloxy) optionally substituted with one or more heteroatoms, mono-, di- or tri-alkylsilyl substituted with 1-6C alkyl or aryl, trifluromethyl, -COM, -COOM, -CH2COOM;

M = H, alkyl optionally substituted with 1-18C;

R11, R12 = H, 1-18C alkyl (optionally substituted), aryl, acyl, methylamino, optionally substituted benzyl, O-glycoside, N-glycoside (mono or disaccharides) or methylene sulfonate;

R2-R5 and R7- R10 = R1 and R6;

R13 = aromatic ring substituted by carboxyl, phosphoryl or sulfonate group(s) or O-glycoside or N-glycoside (mono or disaccharides);

X and Y = O, S, Se or Te; and

R14 = H, 1-18C alkyl substituted by carboxyl, phosphoryl or sulfonate

group(s), optionally substituted aryl, aralkyl or sulfonate. One or more rings of benzene is replaced by N2, the (non)aromatic rings containing heteroatoms are condensed to indirubine system and (I) is bound to polyethylene glycolester or a polyethyleneglycolether. R1 and R5, R6 and R10 form independently from each other a ring having 1-4 CH2 groups.

L20 ANSWER 14 OF 24 WPIDS (C) 2002 THOMSON DERWENT
AN 1999-591435 [51] WPIDS
DNC C1999-172913
TI Treatment of a patient suffering from leukemia or cancer.
DC B02
IN HAJDUCH, M; HAVLICEK, L; STRNAD, M
PA (CESK) AKAD SCI CZECH INST EXPERIMENTAL BOTANY; (HAJD-I) HAJDUCH M; (HAVL-I) HAVLICEK L; (STRN-I) STRNAD M; (CYCL-N) CYCLACEL LTD; (EXPE-N) INST EXPERIMENTAL BOTANY ACAD SCI
CYC 5
PI AU 9856465 A 19990916 (199951)* 24p
CA 2231005 A1 19990904 (200006)# EN
JP 11322610 A 19991124 (200007)# 14p
KR 99073908 A 19991005 (200051)#
US 6221873 B1 20010424 (200125)#
ADT AU 9856465 A AU 1998-56465 19980304; CA 2231005 A1 CA 1998-2231005 19980304; JP 11322610 A JP 1998-123281 19980506; KR 99073908 A KR 1998-7157 19980304; US 6221873 B1 US 1998-34581 19980304
PRAI AU 1998-56465 19980304; CA 1998-2231005 19980304; JP 1998-123281 19980506; KR 1998-7157 19980304; US 1998-34581 19980304
AB AU 9856465 A UPAB: 19991207
NOVELTY - Treatment of a patient suffering from leukemia or cancer comprises administering 2-(((3-hydroxypropyl)amino)-6-benzylamino)-9-isopropylpurine (I), or one of its salts.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for inducing cell death in proliferative cells comprising administration of (I) or 2-(((1-ethyl-2-hydroxyethyl)amino)-6-benzylamino)-9-isopropylpurine (II) or one of their salts.

ACTIVITY - Cytostatic.

Mouse P388D1 leukemia was grown in DMEM (not defined) with glucose (5 g/l), glutamine (2 mM), penicillin (100 U/ml), streptomycin (100 micro g/ml), fetal calf serum (10 %) and sodium bicarbonate up to 80 % confluency. Cells were scraped, and washed and suspended in PBS (not defined) with 0.5 % bovine serum albumin. Cells (0.5 multiply 106) were applied intraperitoneally to DBA-2 mice. One day later, animals were treated with vehicle, (I) (bohemine (BOH)), isopentenyladenine (IP), olomoucine (OC), or roscovitine (ROSC). The compounds were applied in amount 1 mg, subcutaneously, 4 times daily for 7 days. Results are shown in the figure.

MECHANISM OF ACTION - **Cyclin dependent kinase** inhibitor.

USE - The method is used for the treatment of leukemia and cancer.

ADVANTAGE - (I) and (II) inhibit cell proliferation, without inducing changes in gene transcription. (I) and (II) do not inhibit proliferation of healthy tissue.

DESCRIPTION OF DRAWING(S) - The figure shows the results of assays for the evaluation of **antitumor** activity of (I) (bohemine (BOH)), isopentenyladenine (IP), olomoucine (OC), and roscovitine (ROSC) in vivo against murine leukemia P388D1.

Dwg.1a/3
TECH UPTX: 19991207
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Treatment: The leukemia or cancer is not dependent on p53.

The proliferative cells are leukemic or cancer cells. The process works by inhibiting **cyclin dependent kinase 4** (**cdk4**) and/or cdk7 enzymes.

L20 ANSWER 15 OF 24 WPIDS (C) 2002 THOMSON DERWENT
AN 1999-540553 [45] WPIDS
DNC C1999-157848
TI New purine derivatives inhibit cell cycle progression, **cyclin dependent kinases** and development of neoplasms and prevent apoptosis in neuronal cells.
DC B02
IN BITONTI, A J; BORCHERDING, D R; DUMONT, J A; MUNSON, H R; PEET, N P; SHUM, P W; SHUM, P W K
PA (HMRI) HOECHST MARION ROUSSEL INC; (AVET) AVENTIS PHARM INC; (AVET) AVENTIS PHARM CORP
CYC 85
PI WO 9943675 A1 19990902 (199945)* EN 290p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW
ZA 9901551 A 19991124 (200001) 390p
AU 9927709 A 19990915 (200004)
NO 2000004280 A 20001025 (200063)
EP 1056744 A1 20001206 (200064) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
BR 9909256 A 20001128 (200067)
CZ 2000003104 A3 20010117 (200107)
SK 2000001290 A3 20010409 (200131)
CN 1292789 A 20010425 (200143)
KR 2001041318 A 20010515 (200167)
JP 2002504552 W 20020212 (200215) 422p
HU 2001000889 A2 20020128 (200222)
ADT WO 9943675 A1 WO 1999-US3450 19990218; ZA 9901551 A ZA 1999-1551 19990225; AU 9927709 A AU 1999-27709 19990218; NO 2000004280 A WO 1999-US3450 19990218, NO 2000-4280 20000825; EP 1056744 A1 EP 1999-908220 19990218, WO 1999-US3450 19990218; BR 9909256 A BR 1999-9256 19990218, WO 1999-US3450 19990218; CZ 2000003104 A3 WO 1999-US3450 19990218, CZ 2000-3104 19990218; SK 2000001290 A3 WO 1999-US3450 19990218, SK 2000-1290 19990218; CN 1292789 A CN 1999-803397 19990218; KR 2001041318 A KR 2000-709424 20000825; JP 2002504552 W WO 1999-US3450 19990218, JP 2000-533430 19990218; HU 2001000889 A2 WO 1999-US3450 19990218, HU 2001-889 19990218
FDT AU 9927709 A Based on WO 9943675; EP 1056744 A1 Based on WO 9943675; BR 9909256 A Based on WO 9943675; CZ 2000003104 A3 Based on WO 9943675; SK 2000001290 A3 Based on WO 9943675; JP 2002504552 W Based on WO 9943675; HU 2001000889 A2 Based on WO 9943675
PRAI US 1998-30975 19980226
AB WO 9943675 A UPAB: 19991103
NOVELTY - 6,9-Disubstituted 2-(trans-(4-aminocyclohexyl)aminopurine compounds (I) are new.
DETAILED DESCRIPTION - 6,9-Disubstituted 2-(trans-(4-aminocyclohexyl)aminopurine compounds of formula (I) and their salts, optical isomers and hydrates are new.
R = R2, NHR2 or R5NR3R4;
R2 = 9-12C alkyl (optionally substituted by 1-3V), (CR6R6)xOM or (CR6R6)nZ;
M = H, 1-4C alkyl or (CR61R61)x1OQ or (CR61R61)n1Z1;

R6, R61 = H, 3-8C cycloalkyl, 1-4C alkyl or (CH2)m-phenyl;
m, n, n1 = 0-8;
x, x1 = 1-8;
Z = phenyl, heterocyclyl, cycloalkyl or naphthalene all optionally substituted by 1-3 V;
Z1 = phenyl, heterocyclyl, cycloalkyl or naphthalene;
V = D, E, (R62R62)x2S(O)bR62, (R62R62)x2NR62R62, (CR62R62)x2OM1 or (CR62R62)n2Z2;
M1 = H, 1-4C alkyl, (CR63R63)x3OQ1 or (R63R63)n3Z3 all optionally substituted by D1, E1 or (CR64R64)x4OQ2;
D, D1 = CF3, CF3O or 1-4C alkoxy;
E, E1 = halo, OH or 1-8C alkyl;
b = 0-2;
Z2 = phenyl, heterocyclyl, cycloalkyl or naphthalene all optionally substituted by D1, E1 or (CR64R64)x4OQ2;
R62 - R64 = H, 3-8C cycloalkyl, 1-4C alkyl or (CH2)m3-phenyl;
m3, n2, n3 = 0-8;
x3 = 1-8;
Q1 = H or 1-4C alkyl;
Z3 = phenyl, heterocyclyl, cycloalkyl or naphthalene;
R3, R4 = H, 1-4C alkyl, or (CH2)y-phenyl;
y = 0-8;
R5 = 1-8C alkylene;
R1 = cyclopentyl, cyclopentenyl or isopropyl; provided that (i) R3 and R4 are not both H; and (ii) when R2 = (CR6R6)nZ and n is not 0, R1 = isopropyl or cyclopentyl; R6 = H, 1-4C alkyl or (CH2)m-phenyl; then Z = phenyl, heterocyclyl or cycloalkyl substituted by 1-3 D, (R62R62)x2S(O)bR62, (R62R62)x2NR62R62, (CR62R62)x2OM1 or (CR62R62)n2Z2.

INDEPENDENT CLAIMS are also included for:

(i) preventing apoptosis in neuronal cells (no further details are given); and

(ii) a composition comprising an assayable amount of (I) in an inert carrier.

ACTIVITY - Cytostatic.

In cell proliferation assays 2-(trans-(4-aminocyclohexyl)amino)-6-(4-(1-benzyl)piperidinylamino)-9-cyclopentylpurine trihydrochloride (Ia) had the following IC50 values (micro M): MDA-MB-231 (0.17), HT-29 (0.19), DMS-114 (0.12) and DU-145 (0.15). The corresponding values for flavopiridol are 0.095, 0.17, 0.08 and 0.08 respectively.

MECHANISM OF ACTION - CDK-Inhibitor.

USE - For inhibiting cell cycle progression, cyclin dependent kinases (particularly cdk-2) and development of neoplasms and for preventing apoptosis in neuronal cells (e.g. apoptosis induced by antineoplastic agents, cerebrovascular disease, stroke or infarction). (I) are thus useful for treating hyperproliferative disorders (such as neoplastic diseases e.g. chronic leukemia, breast or colon carcinoma, prostate or lung adenocarcinoma, oesteroma, lipoma, melanotic melanoma lymphoid tissue type neoplasm or Hodgkins disease).

Dwg.0/0

TECH UPTX: 19991103

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) are prepared by reacting a 9-substituted -6-amino-2-chloropurine of formula (V) with 1,4-cyclohexanediamine (V).

L20 ANSWER 16 OF 24 WPIDS (C) 2002 THOMSON DERWENT
AN 1999-432548 [37] WPIDS
CR 1999-422070 [36]; 1999-422071 [36]; 1999-520488 [44]
DNN N1999-322084 DNC C1999-127698
TI Diagnosis of cancerous or pre-cancerous cells by monitoring the levels of **cyclin-dependent kinases** 1 and **4**.

DC B04 D16 S03
IN SEABRA, L; WARENIUS, H M
PA (UYLI-N) UNIV LIVERPOOL
CYC 1
PI GB 2334578 A 19990825 (199937)* 26p
ADT GB 2334578 A GB 1998-3447 19980218
PRAI GB 1998-3447 19980218
AB GB 2334578 A UPAB: 19991026
NOVELTY - Diagnosis of a cancerous or pre-cancerous state from the co-elevation of **cyclin-dependent kinase** 1 (CDK1) and **CDK4** levels, is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a kit for diagnosis as above comprising a means for testing the elevation of CDK1 and **CDK4** levels.

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - None given.

USE - The methods and kits may be used for the clinical diagnosis of cancerous or pre-cancerous cells. In addition the combination of targets may be used to **screen** for drugs that may specifically act on cancer cells.

ADVANTAGE - The combination of CDK1. **CDK4** elevation and p53 mutation in combination form a complex target that is likely to be specific for cancerous cells.

Dwg.0/4

TECH UPTX: 19990914
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Sample: The sample to be tested preferably comprises mutant p53 cells.
Preferred Method: Testing comprises contacting the sample with labeled antibodies against CDK1 (preferably sc-54) and/or **CDK4** (preferably sc-260). Mutant p53 cells are identified by using a labeled anti-p53 cell antibody. Testing is carried out by Western blotting, cell count, multi-parameter flow cytometry, scanning confocal microscopy and/or fluorescence activated cell sorting. Prior to the cell count, normal tissue is separated from tumor tissue by micro-dissection, especially using a DNA binding dye (preferably Hoechst 33258 or Chromomycin A3) to label aneuploid cells. The cells are disrupted to form a single cell suspension. The CDK1 and **CDK4** detected are the wild-type forms of the isoenzymes.
Preferred Label: At least one of the antibodies is labeled with a fluorescent label.

L20 ANSWER 17 OF 24 WPIDS (C) 2002 THOMSON DERWENT
AN 1999-422071 [36] WPIDS
CR 1999-422070 [36]; 1999-432548 [37]; 1999-520488 [44]
DNN N1999-315446 DNC C1999-124086
TI Determination of sensitivity of cancer cells to anti-cancer agents.
DC B04 D16 S03
IN SEABRA, L A; WARENIUS, H M; WARENIUS, H
PA (THER-N) THERYTE LTD; (UYLI-N) UNIV LIVERPOOL
CYC 83
PI GB 2334579 A 19990825 (199936)* 44p
WO 9942090 A2 19990826 (199942) EN
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
WO 9942821 A2 19990826 (199942) EN
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL

OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE
GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG
MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG
US UZ VN YU ZW

WO 9942828 A2 19990826 (199942) EN
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE
GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG
MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG
US UZ VN YU ZW

WO 9942834 A2 19990826 (199942) EN
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE
GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG
MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG
US UZ VN YU ZW

WO 9942835 A1 19990826 (199942) EN
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE
GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG
MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG
US UZ VN YU ZW

WO 9942836 A1 19990826 (199942) EN
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE
GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG
MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG
US UZ VN YU ZW

WO 9942837 A1 19990826 (199942) EN
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE
GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG
MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG
US UZ VN YU ZW

WO 9942839 A2 19990826 (199942) EN
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE
GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG
MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG
US UZ VN YU ZW

AU 9925379 A 19990906 (200003)
AU 9925380 A 19990906 (200003)
AU 9925381 A 19990906 (200003)
AU 9925382 A 19990906 (200003)
AU 9925384 A 19990906 (200003)
AU 9925385 A 19990906 (200003)
AU 9926300 A 19990906 (200003)
AU 9926301 A 19990906 (200003)
EP 1057027 A2 20001206 (200064) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
EP 1057028 A1 20001206 (200064) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
EP 1057029 A2 20001206 (200064) EN

R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
EP 1057030 A2 20001206 (200064) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
EP 1057031 A1 20001206 (200064) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
EP 1057032 A2 20001206 (200064) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
EP 1057033 A1 20001206 (200064) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
AU 735896 B 20010719 (200148)
AU 739001 B 20011004 (200166)
AU 741632 B 20011206 (200206)
AU 741712 B 20011206 (200206)
JP 2002503822 W 20020205 (200212) 32p
JP 2002504353 W 20020212 (200215) 30p
JP 2002504354 W 20020212 (200215) 28p
JP 2002504496 W 20020212 (200215) 32p
JP 2002504683 W 20020212 (200215) 32p
JP 2002504687 W 20020212 (200215) 71p
JP 2002504688 W 20020212 (200215) 27p
AU 743454 B 20020124 (200221)

ADT GB 2334579 A GB 1998-14545 19980703; WO 9942090 A2 WO 1999-GB502 19990218; WO 9942821 A2 WO 1999-GB506 19990218; WO 9942828 A2 WO 1999-GB503 19990218; WO 9942834 A2 WO 1999-GB500 19990218; WO 9942835 A1 WO 1999-GB501 19990218; WO 9942836 A1 WO 1999-GB505 19990218; WO 9942837 A1 WO 1999-GB509 19990218; WO 9942839 A2 WO 1999-GB512 19990218; AU 9925379 A AU 1999-25379 19990218; AU 9925380 A AU 1999-25380 19990218; AU 9925381 A AU 1999-25381 19990218; AU 9925382 A AU 1999-25382 19990218; AU 9925384 A AU 1999-25384 19990218; AU 9925385 A AU 1999-25385 19990218; AU 9926300 A AU 1999-26300 19990218; AU 9926301 A AU 1999-26301 19990218; EP 1057027 A2 EP 1999-905081 19990218, WO 1999-GB500 19990218; EP 1057028 A1 EP 1999-905082 19990218, WO 1999-GB501 19990218; EP 1057029 A2 EP 1999-905083 19990218, WO 1999-GB502 19990218; EP 1057030 A2 EP 1999-905084 19990218, WO 1999-GB503 19990218; EP 1057031 A1 EP 1999-905086 19990218, WO 1999-GB505 19990218; EP 1057032 A2 EP 1999-905087 19990218, WO 1999-GB506 19990218; EP 1057033 A1 EP 1999-906326 19990218, WO 1999-GB509 19990218; AU 735896 B AU 1999-25381 19990218; AU 739001 B AU 1999-25380 19990218; AU 741632 B AU 1999-25384 19990218; AU 741712 B AU 1999-25382 19990218; JP 2002503822 W WO 1999-GB502 19990218, JP 2000-532107 19990218; JP 2002504353 W WO 1999-GB503 19990218, JP 2000-532719 19990218; JP 2002504354 W WO 1999-GB509 19990218, JP 2000-532728 19990218; JP 2002504496 W WO 1999-GB501 19990218, JP 2000-532726 19990218; JP 2002504683 W WO 1999-GB506 19990218, JP 2000-532712 19990218; JP 2002504687 W WO 1999-GB500 19990218, JP 2000-532725 19990218; JP 2002504688 W WO 1999-GB505 19990218, JP 2000-532727 19990218; AU 743454 B AU 1999-25379 19990218

FDT AU 9925379 A Based on WO 9942834; AU 9925380 A Based on WO 9942835; AU 9925381 A Based on WO 9942090; AU 9925382 A Based on WO 9942828; AU 9925384 A Based on WO 9942836; AU 9925385 A Based on WO 9942821; AU 9926300 A Based on WO 9942837; AU 9926301 A Based on WO 9942839; EP 1057027 A2 Based on WO 9942834; EP 1057028 A1 Based on WO 9942835; EP 1057029 A2 Based on WO 9942090; EP 1057030 A2 Based on WO 9942828; EP 1057031 A1 Based on WO 9942836; EP 1057032 A2 Based on WO 9942821; EP 1057033 A1 Based on WO 9942837; AU 735896 B Previous Publ. AU 9925381, Based on WO 9942090; AU 739001 B Previous Publ. AU 9925380, Based on WO 9942835; AU 741632 B Previous Publ. AU 9925384, Based on WO 9942836; AU 741712 B Previous Publ. AU 9925382, Based on WO 9942828; JP 2002503822 W Based on WO 9942090; JP 2002504353 W Based on WO 9942828; JP 2002504354 W Based on WO 9942837; JP 2002504496 W Based on WO 9942835; JP 2002504683 W Based on WO 9942821; JP 2002504687 W Based on WO 9942834; JP 2002504688 W

Based on WO 9942836; AU 743454 B Previous Publ. AU 9925379, Based on WO 9942834

PRAI GB 1998-12151 19980605; GB 1998-3446 19980218; GB 1998-3447 19980218; GB 1999-3035 19990210

AB GB 2334579 A UPAB: 20020403

NOVELTY - Determination of sensitivity of cancer cells to anti-cancer agents by measuring the mutational status, expression and /or function of signal transduction factors is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for:

(1) a method of measuring the sensitivity of a cancer cell to an anti-cancer agent, which comprises testing a sample for the mutational status, expression, and/or function of a negative signal transduction factor (NSTF), and the mutational status, expression, and/or function of a positive signal transduction factor (PSTF); the method does not comprise measuring the radiosensitivity of wild-type p53 cancer cells by testing a sample comprising wild-type p53 for the abundance of Raf-1 protein other than by employing an antibody specific to Raf-1 protein, and

(2) a kit for measuring the sensitivity of a cancer cell to an anti-cancer agent.

USE - The method, by measuring the resistance of cells to anti-cancer agents, is useful for selecting the most appropriate therapy for patients suffering from cancer.

Dwg.0/7

TECH UPTX: 19990908

TECHNOLOGY FOCUS - BIOTECHNOLOGY - The NSTF is a suppressor, especially p53, p21 or an inhibitor which inhibits or arrests the cell cycle and/or causes apoptosis. The NSTF may be a PSTF inhibitor e.g. a Raf-1 inhibitor, a cyclin D1 inhibitor or a **cyclin dependent kinase** inhibitor.

The PSTF is a factor which stimulates cells to enter the cell cycle, initiates and/or carries out DNA synthesis, and/or controls the passage of cells through the cell cycle. The PSTF is an oncogene, a proto-oncogene, a gene which inhibits and/or controls cell cycle division, or a cell surface receptor. The PSTF is especially a Raf-1 protein, a cyclin D1 protein or a **cyclin dependent kinase**, such as CDK1 or **CDK4**.

The **anticancer** agent is ionising radiation, or a molecular anti-cancer agent such as a chemotherapeutic agent, e.g. a platinating agent, which is especially cisdiamminedichloroplatinum (CDDP), or a biological cancer therapy agent.

L20 ANSWER 18 OF 24 WPIDS (C) 2002 THOMSON DERWENT

AN 1999-395087 [33] WPIDS

DNC C1999-116126

TI Pyrazolo pyridine compound **cyclin dependent kinase** inhibitors, used e.g. for treating cancer, inflammation or viral or fungal infection.

DC B02 C02

IN BURSUKER, I; KIMBALL, S D; MISRA, R N; RAWLINS, D B; WEBSTER, K R

PA (BRIM) BRISTOL-MYERS SQUIBB CO

CYC 83

PI WO 9930710 A1 19990624 (199933)* EN 40p

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW

W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW

AU 9916297 A 19990705 (199948)

US 6107305 A 20000822 (200042)

ZA 9811178 A 20000830 (200049) 45p
EP 1043998 A1 20001018 (200053) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
JP 2002508324 W 20020319 (200222) 46p
ADT WO 9930710 A1 WO 1998-US25920 19981207; AU 9916297 A AU 1999-16297 19981207; US 6107305 A Provisional US 1997-69633P 19971213, US 1998-209575 19981211; ZA 9811178 A ZA 1998-11178 19981207; EP 1043998 A1 EP 1998-960781 19981207, WO 1998-US25920 19981207; JP 2002508324 W WO 1998-US25920 19981207, JP 2000-538693 19981207
FDT AU 9916297 A Based on WO 9930710; EP 1043998 A1 Based on WO 9930710; JP 2002508324 W Based on WO 9930710
PRAI US 1997-69633P 19971213; US 1998-209575 19981211
AB WO 9930710 A UPAB: 19990819
NOVELTY - The use of pyrazolo (3,4-b) pyridine compounds (I) as inhibitors of **cyclin dependent kinases** is new.

DETAILED DESCRIPTION - Pyrazolo (3,4-b) pyridine compounds of formula (I) and their salts are claimed for use as inhibitors of **cyclin dependent kinases**.

X = O or S(O)m;

Y, R2 = alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

R1, R3 = H or 1-6C alkyl;

R2 = alkyl, aryl, arylalkyl, heteroaryl, heteroaryl alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, alkoxy, aryloxy or -NR4R5;

R4 = H, alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, alkoxy or aryloxy;

R5 = H, alkyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl, cycloalkyl, alkylcycloalkyl, heterocycloalkyl, alkylheterocycloalkyl, alkoxy or aryloxy;

m = 0-2;

alkyl moieties = 1-12C and cycloalkyl moieties = 3-15C unless specified otherwise.

INDEPENDENT CLAIMS are included for pharmaceutical compositions (not restricted to the above activity) containing (I) and a carrier; and methods for inhibiting protein kinases or **cyclin dependent kinases** involving administration of (I).

ACTIVITY - Antiproliferative; **anticancer**; antiinflammatory; antiarthritic; antiviral; antifungal; neuroprotective; apoptosis modulator; cellular nucleic acid synthesis modulator.

MECHANISM OF ACTION - Protein kinase inhibitor; **cyclin dependent kinase** inhibitor. Specifically (I) inhibit cdc2 (cdk1), cdk2, cdk3, **cdk4**, cdk5, cdk6, cdk7 and cdk8. (4-Butoxy-1H-pyrazolo (3,4-b) pyridin-5-yl) (2,4,6-trifluorophenyl) methanone (Ia) inhibited cdc2/cyclin B1 kinase activity with an IC50 value of less than 50 mu M.

USE - For treating proliferative diseases, cancer, inflammation, inflammatory bowel disease, transplantation rejection, arthritis, viral infections (specifically human immunodeficiency virus (HIV) infection), fungal infections and neurodegenerative disease; for treating or preventing the development of AIDS; and for preventing the development of cancer or tumor relapse (all claimed).

Neurodegenerative disease includes Alzheimer's disease, Parkinson's disease or amyotrophivc lateral sclerosis. Other disclosed diseases which may be treated include cardiovascular disease (e.g. restenosis or atherosclerosis), benign prostatic hyperplasia, neuro-fibromatosis, pulmonary fibrosis, psoriasis, endotoxic shock, autoimmune diseases (e.g. systemic lupus erythematosus or autoimmune diabetes mellitus), liver disease, anemia, osteoporosis, cystic fibrosis, multiple sclerosis, kidney

disease and cancer pain.
Dwg.0/0

TECH UPTX: 19990819
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) are prepared e.g. by introduction of the group -X-Y by nucleophilic substitution of the corresponding 4-chloro compound.

L20 ANSWER 19 OF 24 WPIDS (C) 2002 THOMSON DERWENT
AN 1999-357351 [30] WPIDS
DNC C1999-105653
TI New immunogenic compositions for treating cancer or virus or parasite infection.
DC A96 B04 D16
IN BRASLAWSKY, G R; HANNA, N; HARIHARAN, K; HARIHARA, K
PA (IDEC-N) IDEC PHARM CORP
CYC 84
PI WO 9913912 A1 19990325 (199930)* EN 41p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW
ZA 9808461 A 19990630 (199931) 36p
AU 9895658 A 19990405 (199933)
EP 1015031 A1 20000705 (200035) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
NO 2000001413 A 20000518 (200035)
CN 1279616 A 20010110 (200128)
US 2001018054 A1 20010830 (200151)
US 2001019715 A1 20010906 (200154)
KR 2001024109 A 20010326 (200161)
JP 2001516727 W 20011002 (200172) 32p
AU 742216 B 20011220 (200208)
ADT WO 9913912 A1 WO 1998-US18495 19980917; ZA 9808461 A ZA 1998-8461 19980916; AU 9895658 A AU 1998-95658 19980917; EP 1015031 A1 EP 1998-949313 19980917, WO 1998-US18495 19980917; NO 2000001413 A WO 1998-US18495 19980917, NO 2000-1413 20000317; CN 1279616 A CN 1998-811280 19980917; US 2001018054 A1 Cont of US 1997-933359 19970918, US 2001-853580 20010514; US 2001019715 A1 Div ex US 1997-933359 19970918, US 2001-853581 20010514; KR 2001024109 A KR 2000-702864 20000317; JP 2001516727 W WO 1998-US18495 19980917, JP 2000-511527 19980917; AU 742216 B AU 1998-95658 19980917
FDT AU 9895658 A Based on WO 9913912; EP 1015031 A1 Based on WO 9913912; JP 2001516727 W Based on WO 9913912; AU 742216 B Previous Publ. AU 9895658, Based on WO 9913912
PRAI US 1997-933359 19970918; US 2001-853580 20010514; US 2001-853581 20010514
AB WO 9913912 A UPAB: 19990802
NOVELTY - New immunogenic compositions for treating cancer or virus or parasite infection comprise a combination of antigen formulation and an agent capable of neutralizing or down-regulating immunosuppressive factors.
DETAILED DESCRIPTION - A composition (A) comprises:
(a) an admixture comprising a cancer, viral or parasitic antigen expressed by cancer, virally or parasitic infected cells and a microfluidized antigen formulation (MAF) (formulated as a stable oil-in-water emulsion), the antigen formulation comprising:
(i) a stabilizing detergent;
(ii) a micelle-forming agent; and

(iii) a biodegradable and biocompatible oil; and

(b) at least one agent which is capable of neutralizing or down-regulating the activity of immunosuppressive factors.

INDEPENDENT CLAIMS are also included for the following:

(1) a method of treatment which includes the induction of a cytotoxic T-lymphocyte (CTL) response where the improvement comprises:

(a) the administration of an adjuvant which induces a CTL response; and

(b) the administration of an antagonist of an immunosuppressive factor, where the administration of adjuvant and antagonist is effected sequentially or concurrently, and in any order;

(2) a method of restoring or boosting hematopoiesis comprising administering to a patient:

(a) an admixture as in (A) (a) which is administered to the patient to induce a CTL response in the patient which is specific for the viral or cancer antigen contained in the admixture; and

(b) at least one agent which is capable of neutralizing or down regulating the activity of tumor and host secreted immunosuppressive factors, where the admixture and the agent are administered separately or in combination, and in any order;

(3) a composition comprising an admixture as in (A) (a) and one or more transforming growth factor (TGF) beta antagonists;

(4) treatment of neoplastic or cancerous growths, comprising:

(a) administration of an admixture comprising a cancer or tumor antigen expressed by the cancer cells and a MAF (described above); and

(b) administration of at least one agent which is capable of neutralizing or down-regulating the activity of tumors and host secreted immunosuppressive factors. The admixture is administered in an amount sufficient to induce a cytotoxic T-lymphocyte response in the patient which is specific for the cancer or tumor antigen contained in the admixture.

ACTIVITY - **Antitumor**; Antiviral; Antiparasitic.

MECHANISM OF ACTION - Induction of a cytotoxic T-lymphocyte response.

USE - The methods can be used for restoring or boosting hematopoiesis (claimed). They can be used for treating cancers, e.g. breast cancer, brain cancer, cervical cancer, leukemia, lymphoma, prostate cancer, skin cancer, bladder cancer, kidney cancer, myeloma, colorectal cancer, or endometrial cancer, viral infections e.g. papillomavirus, hepatitis, herpes, cytomegalovirus, respiratory syncytial virus or HIV, or parasitic infection, e.g. malaria (claimed). The agent which is capable of neutralizing or down-regulating the activity of immunosuppressive factors enhances the efficacy of tumor/viral vaccines.

ADVANTAGE - The combinations of the antigen compositions and antagonists of immunosuppressive agents results in a synergistic enhancement of CTL response, thereby resulting in enhanced therapeutic response against targeted antigen-expressing cells.

Dwg.0/4

TECH UPTX: 19990802

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Composition: The detergent may be e.g. Tween 80 (RTM), Tween 20 (RTM), Tween 40 (RTM), Tween 60 (RTM), Zwittergent 3-12 (RTM), Teepol HB7, or SPAN 85. The amount of detergent is 0.05-0.5%.

The micelle-forming agent has a hydrophilic-lipophilic balance of 0-2 and may be e.g. Poloxamer 401 (RTM), Puronic L62Lf (RTM), Pluronic L101 (RTM), Pluronic L64, PEG1000 (RTM), Tetronic 1501 (RTM), Tetronic 150R1 (RTM), Tetronic 701 (RTM), Tetronic 901, Tetronic 1301, Tetronic 130R1 (RTM). The amount of this agent is 0.5-10%.

The oil has a melting point of below 65degreesC and may be e.g. squalene, eicosane, tetratetracontane, pristane, or a vegetable oil (especially olive oil). The amount of oil is 2.5-5%.

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Composition: The immunosuppressive factor is transforming growth factor beta (TGFbeta). The agent which is capable of neutralizing or down-regulating the activity of tumor or host secreted immunosuppressive factors may be e.g. an anti-TGF-beta antibody, a TFGbetaR-fusion protein, a TGF-beta analog, a TGF-beta binding protein, a TGF-betaR blocking antibody, a thrombospondin peptide, a TFGbetaR Fc-fusion protein. The antigen may be e.g. gp100, MART-1/Melan A, gp75, tyrosinase, melanoma proteoglycan, MAGE, BAGE, GAGE, RAGE, N-acetylglucosaminyltransferase-V, **mutated** beta-**catenin**, **mutated** MUM-1, **mutated cyclin dependent kinases-4**, p21 ras, BCR-abl, p53, p185 HER2/neu, mutated epidermal growth factor receptor, carcinoembryonic antigens, carcinoma associated mutated mucins, EBNA gene products, papillomavirus E7 protein, papillomavirus E6 protein, prostate specific antigens, prostate specific membrane antigen, PCTA-1, immunoglobulin idiotypes or T cell receptor idiotypes.

L20 ANSWER 20 OF 24 WPIDS (C) 2002 THOMSON DERWENT
AN 1999-326677 [27] WPIDS
DNC C1999-096616
TI 4-Aminothiazoles, their salts, prodrugs and active metabolites, used to treat proliferative disorders.
DC B03
IN CHONG, W K M; CHU, S S; DUVADIE, R R; LI, L; XIAO, W; YANG, Y; DUVADIE, R K; CHONG, K M W
PA (AGOU-N) AGOURON PHARM INC
CYC 83
PI WO 9921845 A2 19990506 (199927)* EN 172p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9913664 A 19990517 (199939)
NO 2000001955 A 20000616 (200040)
EP 1056732 A2 20001206 (200064) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
CZ 2000001285 A3 20010117 (200107)
CN 1276789 A 20001213 (200118)
SK 2000000521 A3 20010409 (200131)
MX 2000003812 A1 20001101 (200163)
AU 738792 B 20010927 (200170)
BR 9815200 A 20011016 (200170)
KR 2001082501 A 20010830 (200215)
ADT WO 9921845 A2 WO 1998-US22809 19981027; AU 9913664 A AU 1999-13664 19981027; NO 2000001955 A WO 1998-US22809 19981027, NO 2000-1955 20000414; EP 1056732 A2 EP 1998-957393 19981027, WO 1998-US22809 19981027; CZ 2000001285 A3 WO 1998-US22809 19981027, CZ 2000-1285 19981027; CN 1276789 A CN 1998-810474 19981027; SK 2000000521 A3 WO 1998-US22809 19981027, SK 2000-521 19981027; MX 2000003812 A1 MX 2000-3812 20000418; AU 738792 B AU 1999-13664 19981027; BR 9815200 A BR 1998-15200 19981027, WO 1998-US22809 19981027; KR 2001082501 A KR 2000-704392 20000422
FDT AU 9913664 A Based on WO 9921845; EP 1056732 A2 Based on WO 9921845; CZ 2000001285 A3 Based on WO 9921845; SK 2000000521 A3 Based on WO 9921845; AU 738792 B Previous Publ. AU 9913664, Based on WO 9921845; BR 9815200 A Based on WO 9921845
PRAI US 1997-63666P 19971028; US 1997-63634P 19971027

AB WO 9921845 A UPAB: 20011203
NOVELTY - 4-Aminothiazole derivatives, their salts, prodrugs and active metabolites are new.

DETAILED DESCRIPTION - 4-Aminothiazole derivatives of formula (I) are new:

R1 = 1-6C alkyl, 1-6C alkenyl, 1-6C alkynyl, 1-6C alkoxy, 1-6C alcohol, carbocyclic or heterocyclic, monocyclic, (non)-fused polycyclic cycloalkyl or aryl, carbonyl, ether, 1-6C alkylcarbonyl, 1-6C alkylaryl, 1-6C alkylcycloalkyl, 1-6C alkyl-(1-6C) alkoxy, aryl-(1-6C) alkoxy, thioether, thiol or sulfonyl (all optionally substituted by halo, haloalkyl, 1-6C alkyl, 1-6C alkenyl, 1-6C alkynyl, hydroxy, 1-6C alkoxy, amino, nitro, thiol, thioether, imine, cyano, amido, phosphonato, phosphine, carboxyl, thiocarbonyl, sulfonyl, sulfonamido, ketone, aldehyde, ester, oxygen (sic), carbocyclic or heterocyclic, mono or (non)fused polycyclic cycloalkyl or aryl);

R2 = carbocyclic or heterocyclic, monocyclic or (non)fused polycyclic ring with a substituent at the position adjacent to the point of attachment and optionally further substituted by halo, haloalkyl, 1-6C alkyl, 1-6C alkenyl, 1-6C alkynyl, hydroxy, 1-6C alkoxy, amino, nitro, thiol, thioether, imine, cyano, amido, phosphonato, phosphine, carboxyl, thiocarbonyl, sulfonyl, sulfonamido, ketone, aldehyde, ester, oxygen (sic), carbocyclic or heterocyclic, mono or (non)fused polycyclic cycloalkyl or aryl.

ACTIVITY - Cell cycle control; cytotoxic; **anticancer**; anti-mycotic; anti-proliferative.

Inhibition of cell growth was measured by a tetrazolium salt assay. HCT-116 cell line was grown in 96-well plates in 135 micro l/well McCoy's 5A medium. Plates were incubated for 4 hours before addition of inhibitor compounds. Different concentrations were added in 0.5% dimethylsulfoxide (DMSO; 15 micro l/well) and incubated at 37 deg. C (5% carbon dioxide) for 4-6 days. At the end of the incubation, 3-(4,5-dimethylthiazol-2-yl)-2,5-(2H)-diphenyltetrazolium bromide (MTT) was added to make a final concentration of 0.2 mg/ml and cells were incubated for 4 hours at 37 deg. C. After centrifugation of the plates and removal of the medium, the absorbance of formazan solubilized in dimethylsulfoxide was measured at 540 nm. The concentration of inhibitor compound causing 50% growth was determined from the linear portion of a semi-log plot of inhibitor concentration versus percentage inhibition. All results were compared to control cells treated with only 0.5% volume/volume DMSO. IC50 values ere 0.3 micro M for (4-amino-2-phenylaminothiazol-5-yl)-(3-nitrophenyl)-methanone (Ia) and 0.7 micro M for (4-(N,N-dimethyl)amino-2-phenylaminothiazol-5-yl)-(3-nitrophenyl)-methanone (Ib).

MECHANISM OF ACTION - **Cyclin-dependent kinase** (CDK) inhibitor; CDK2 inhibitor; **CDK4** inhibitor; CDK6 inhibitor; **CDK4**/D-type cyclin complex inhibitor; **CDK4**/E-type cyclin complex inhibitor.

Complex of human **CDK4** and cyclin D3, a complex of cyclin D1 and a fusion protein of human **CDK4** and glutathione-S-transferase (GST-**CDK4**) or a complex of human **CDK4** and genetically truncated (1-264) cyclin D3 was purified using traditional biochemical chromatographic techniques from insect cells co-infected with the corresponding baculovirus expression vectors. The enzyme complex (5 or 50 nM) was assayed with 0.3-0.5 micro g of purified recombinant retinoblastoma protein fragment (Rb) as a substrate. The engineered Rb fragment (residues 386-928) of the native retinoblastoma protein; 62.3 kDa) contained the majority of the phosphorylation sites found in the native 106 kDa protein as well as a tag of six histidine residues for ease of purification. Phosphorylated Rb substrate was captured by microfiltration on a nitrocellulose membrane and quantified using a phosphoimager. For measurement of tight-biding enzymes, the enzyme complex

concentration was lowered to 5 nM and the assay duration extended to 60 minutes, during which the time-dependence of product formulation was linear. Apparent Ki values were measured by assaying enzyme activity in the presence of different inhibitor compound concentrations and subtracting the background radioactivity measured in the absence of enzyme. **CDK** 4/cyclin D3 Ki values were 660 nM for (4-amino-2-phenylaminothiazol-5-yl)-(3-nitrophenyl)-methanone (Ia) and 95 nM for (4-(N,N-dimethyl)amino-2-phenylaminothiazol-5-yl)-(3-nitrophenyl)-methanone (Ib).

USE - Used for treatment of disorders or diseases mediated by inhibition of **CDK4** or **CDK4**/cyclin complex (claimed) including malignancies by blocking transition of cancer cells into their proliferative phase. Also used for prevention or treatment of mycotic infections. Used to treat proliferative disorders in mammals, especially humans, marked by unwanted proliferation of endogenous tissue including cancers, psoriasis, immunological disorders involving undesired proliferation of leukocytes, restenosis and other smooth-muscle disorders, and to prevent de-differentiation of post-mitotic tissue and/or cells.

TECH UPTX: 19990714

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: No general methods of preparation are given but compounds (I) can be made by e.g. reacting phenyl isocyanate and cyanamide and adding 2-bromo-4'-nitroacetophenone to the reaction mixture.

L20 ANSWER 21 OF 24 WPIDS (C) 2002 THOMSON DERWENT
AN 1999-313169 [26] WPIDS
DNC C1999-092489
TI Composition containing inhibitor of proteasome.
DC B05
IN WANG, X; WU, J
PA (UYMO-N) UNIV MONTREAL CENT RECH CENT HOSPITALIER; (WANG-I) WANG X; (WUJJ-I) WU J
CYC 83
PI WO 9922729 A1 19990514 (199926)* EN 105p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9897318 A 19990524 (199940)
CA 2219867 A1 19990430 (199941) EN
EP 967976 A1 20000105 (200006) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
JP 2001508465 W 20010626 (200140) 98p
ADT WO 9922729 A1 WO 1998-CA1010 19981029; AU 9897318 A AU 1998-97318 19981029; CA 2219867 A1 CA 1997-2219867 19971031; EP 967976 A1 EP 1998-951135 19981029, WO 1998-CA1010 19981029; JP 2001508465 W WO 1998-CA1010 19981029, JP 1999-525054 19981029
FDT AU 9897318 A Based on WO 9922729; EP 967976 A1 Based on WO 9922729; JP 2001508465 W Based on WO 9922729
PRAI CA 1997-2219867 19971031
AB WO 9922729 A UPAB: 20011203

NOVELTY - Composition for (i) reversing an on-going adverse immune response, (ii) disrupting mitochondrial function or (iii) disrupting nitric oxide synthesis contains a proteasome inhibitor (I).

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a method of **screening** for (I) by treating a mammalian cell lysate that contains proteasomes with a labeled peptide substrate; treating the mixture with a test compound and measuring the amount of label released

from the substrate, in presence and absence of test compound. Absence, or reduction in the amount, of released label shows the test compound to be an inhibitor.

ACTIVITY - Immunosuppressant; **anticancer**; anti-inflammatory.

MECHANISM OF ACTION - (I) (i) reduces activation of T cells; (ii) disrupts mitochondrial function by blocking electron transport and/or inducing cytochrome C leakage from the mitochondria, resulting in caspase activation and apoptosis; (iii) inhibits nitric oxide synthase. The proteasome is essential for (i) progression of T cells from the G0 to S1 phases; (ii) for electron transport in mitochondria; (iii) for upregulation of interleukin-1receptor alpha ; (iv) for function of **cyclin-dependent kinase** (CDK) 2 but not **CDK4**; (v) for degradation of cyclin E but not cyclin A.

USE - (I) is used (a) to treat autoimmune disease and graft rejection, administered after activation of T cells: (b) to treat diseases associated with high mitochondrial activity, especially cancer, inflammation, adverse immune reactions and hyperthyroidism and (c) to treat conditions associated with expression of nitric oxide synthase, particularly inflammation and septic shock.

ADVANTAGE - (I) induce apoptosis in activated (leukemic or antigen specific), but not resting, T cells. The effect of (I) is rapid and reversible. T cells, either resting or stimulated 40 hr earlier with phytohemagglutinin, were cultured in presence of 10 micro M lactocystin, and after a further 24 hr analyzed for viability by trypan blue exclusion. Viability for the stimulated cells was only 46% of that for untreated controls, but for treated, resting cells viability was 87% of that for the controls.

TECH UPTX: 19990707

TECHNOLOGY FOCUS - BIOLOGY - Preferred process: In the **screening** method, the substrate is a fluorogenic peptide and the proteasome proteinase activity being monitored is a trypsin-like, chymotrypsin-like or peptidylglutamyl-peptide hydrolyzing activity.

L20 ANSWER 22 OF 24 WPIDS (C) 2002 THOMSON DERWENT
AN 1999-263461 [22] WPIDS
DNC C1999-077660
TI New substituted oxindole derivatives.
DC B02
IN DAVIS, S T; DICKERSON, S H; FRYE, S V; HARRIS, P A; HUNTER, R N; KUYPER, L F; LACKEY, K E; LUZZIO, M J; VEAL, J M; WALKER, D H
PA (GLAX) GLAXO GROUP LTD; (SMIK) SMITHKLINE BEECHAM CORP
CYC 84
PI WO 9915500 A1 19990401 (199922)* EN 133p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9897407 A 19990412 (199934)
ZA 9808078 A 20000531 (200032) 130p
EP 1009738 A1 20000621 (200033) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
CZ 2000000798 A3 20000816 (200048)
BR 9812048 A 20000926 (200051)
CN 1278794 A 20010103 (200124)
HU 2000004490 A2 20010328 (200124)
MX 2000002254 A1 20001001 (200158)

KR 2001023695 A 20010326 (200161)
JP 2001517652 W 20011009 (200174) 200p
US 6369086 B1 20020409 (200227)

ADT WO 9915500 A1 WO 1998-EP5559 19980903; AU 9897407 A AU 1998-97407 19980903; ZA 9808078 A ZA 1998-8078 19980903; EP 1009738 A1 EP 1998-951342 19980903, WO 1998-EP5559 19980903; CZ 2000000798 A3 WO 1998-EP5559 19980903, CZ 2000-798 19980903; BR 9812048 A BR 1998-12048 19980903, WO 1998-EP5559 19980903; CN 1278794 A CN 1998-810937 19980903; HU 2000004490 A2 WO 1998-EP5559 19980903, HU 2000-4490 19980903; MX 2000002254 A1 MX 2000-2254 20000303; KR 2001023695 A KR 2000-702348 20000304; JP 2001517652 W WO 1998-EP5559 19980903, JP 2000-512809 19980903; US 6369086 B1 CIP of WO 1998-EP5559 19980903, US 1999-262351 19990304

FDT AU 9897407 A Based on WO 9915500; EP 1009738 A1 Based on WO 9915500; CZ 2000000798 A3 Based on WO 9915500; BR 9812048 A Based on WO 9915500; HU 2000004490 A2 Based on WO 9915500; JP 2001517652 W Based on WO 9915500

PRAI GB 1997-18913 19970905

AB WO 9915500 A UPAB: 20011203

NOVELTY - Substituted oxindole derivatives (I) are new.

DETAILED DESCRIPTION - Substituted oxindole derivatives of formula (I) and their salts, biohydrolyzable esters, biohydrolyzable amides or carbamates, solvates, hydrates, affinity reagents or prodrugs in either crystalline or amorphous form are new:

X = N, CH, CCF3 or C(1-12C aliphatic);

R1 = H, 1-12C aliphatic, thiol, hydroxy, hydroxy-(1-12C aliphatic), Aryl, Aryl-(1-12C) aliphatic, R6-Aryl-(1-12C) aliphatic, Cyc, Cyc-1-6C aliphatic, Het, Het-(1-12C) aliphatic, 1-12C alkoxy, Aryloxy, amino, 1-12C aliphatic-amino, di-(1-12C) aliphatic-amino, di-(1-12C) aliphatic aminocarbonyl, di-(12C) aliphatic-aminosulfonyl, 1-12C alkoxycarbonyl, halo, cyano, sulfonamide or nitro;

R2 = H, 1-12C aliphatic, N-hydroxyimino-(1-12C) aliphatic, 1-12C alkoxy, hydroxy-(1-12C) aliphatic, 1-12C alkoxycarbonyl, carboxyl-(1-12C) aliphatic, Aryl, R6-Aryl-oxycarbonyl, R6-oxycarbonyl-Aryl, Het, aminocarbonyl, 1-12C aliphatic-aminocarbonyl, Aryl-(1-12C) aliphatic aminocarbonyl, R6-Aryl-(1-12C) aliphatic-aminocarbonyl, Het-(1-12C) aliphatic-aminocarbonyl, hydroxy-(1-12C) aliphatic-aminocarbonyl, 1-12C alkoxy-(1-12C) aliphatic-aminocarbonyl, 1-12C alkoxy-(1-12C) aliphatic-amino, di-(1-12C) aliphatic-amino, di-(1-12C) aliphatic-aminocarbonyl, di-(1-12C) aliphatic-aminosulfonyl, halo, hydroxy, nitro, 1-12C aliphatic-sulfonyl, aminosulfonyl or 1-12C aliphatic-aminosulfonyl; or

R1 + R2 = a fused ring chosen from Het (optionally substituted by halo, nitro, cyano, 1-12C alkoxy, carbonyl-(1-12C) alkoxy or oxo);

R3 = H, 1-12C aliphatic, hydroxy, hydroxy(1-12C) aliphatic, di-(1-12C) aliphatic-amino, di-(1-12C) aliphatic-aminocarbonyl, di(1-12C) aliphatic-aminosulfonyl, 1-12C alkoxy, Aryl, Aryloxy, hydroxyl-Aryl, Het, hydroxy-Het, Het-oxy or halo; or

R2 + R3 = a fused ring chosen from Het (optionally substituted by 1-6C aliphatic or 1-6C aliphatic carbonyl;

R4 = sulfonic acid, 1-12C aliphatic sulfonyl, sulfonyl-(1-12C) aliphatic, 1-12C aliphatic sulfonyl(-16C) aliphatic, 1-6C aliphatic-amino, R7-sulfonyl, R7-sulfonyl(1-12C) aliphatic, R7-aminosulfonyl, R7-aminosulfonyl-(1-12C) aliphatic, R7-sulfonylamino, R7-sulfonylamino-(1-12C) aliphatic, aminosulfonylamino, di-(1-12C) aliphatic-amino, di-(1-12C) aliphatic-aminocarbonyl, di-(1-12C) aliphatic-aminosulfonyl, di-(1-12C) aliphatic-amino, di-(1-12C) aliphatic-amino-(1-12C) aliphatic, (R8)1-3-Aryl-amino, (R8)n-Aryl-sulfonyl, (R8)n-Aryl-aminosulfonyl, (R8)n-Aryl-sulfonylamino, Het-amino, Het-sulfonyl, Het-aminosulfonyl, aminoiminoamino or aminoiminoaminosulfonyl;

n = 1-3;

R5 = H; or

R4 and R5 = Het (optionally substituted by 1-12C aliphatic, oxo or dioxo);

R6 = 1-12C aliphatic, hydroxy, 1-12C alkoxy or halo;

R7 = H, 1-12C aliphatic, 1-12C alkoxy, hydroxy-(1-12C) alkoxy, hydroxy-(1-12C) aliphatic, carboxylic acid, 1-12C aliphatic carbonyl, Het, Het-(1-12C) aliphatic, Het-(1-12C) alkoxy, di-Het-(1-12C)alkoxy-Aryl, Aryl-(1-12C)aliphatic, Aryl-(1-12C)alkoxy, Aryl-carbonyl, 1-18C alkoxyalkoxyalkoxyalkoxyaliphatic or hydroxyl;

R8 = H, nitro, cyano, 1-12C alkoxy, halo, carbonyl-(1-12C) alkoxy or halo-(1-12C) aliphatic;

Aryl = phenyl, naphthyl, phenanthryl or anthracenyl;

aliphatic = alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene (disclosed);

Cyc = cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl (all optionally unsaturated); and

Het = optionally saturated heterocycle chosen from benzimidazole, didhydrothiophene, dioxin, dioxane, dioxolane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, morpholine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, piperazine, piperidine, pyran, pyrazine, pyrazole, pyridine, pyrimidine, pyrrole, pyrrolidine, tetrahydrofuran, tetrazine, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thiophene, thiopyran, triazine or triazole.

provided that:

(a) R1-R3 may not all be H; and

(b) when R2 = thiadiazine, R4 cannot be methylsulfone.

ACTIVITY - Immunosuppressant, **anticancer**, anti-arthritic, anti-angiogenic, anti-cirrhotic, anti-atherosclerotic, renal, anti-psoriatic, anti-diabetic, anti-inflammatory, neuroactive, anti-hyperproliferative.

MECHANISM OF ACTION - Protein kinase inhibitor; protein kinase antagonist.

CDK1 and CDK2 were expressed using a baculovirus expression system and were purified partially to comprise 20-80% of total protein with no detectable competing reactions present. Assays were performed by incubating either enzyme (0.2-10 nM), with and without inhibitor, one of the two peptide substrates (1-10 nM), (gamma 32P)ATP (1-120 nM) and magnesium ions (10-20 nM) for 10-120 minutes. Reactions were terminated with 0.2-2 volumes of either acetic acid or 50-100 mM EDTA buffered to pH 7. The buffer employed was either 30 mM HEPES 7.4 containing 0.15 M sodium chloride and 5% dimethylsulfoxide (DMSO), the buffer 50 M MOPS 7.0 containing 0.15M sodium chloride and 5% DMSO or the buffer 100 mM HEPES 7.5 containing 0.1 mg/ml bovine serum albumin and 5% DMSO. Inhibitors were diluted in 100% DMSO prior to addition into the assay. Detection of peptide phosphorylation was accomplished by scintillation counting. Counts detected minus the appropriate background (assays with additional 40 mM EDTA or lacking peptide substrate) were assumed to be proportional to the reaction initial rates and IC50 values were determined by a least squares fit to the equation CPM = Vmax asterisk (1-(I)/(K+(I)))+nsb. Twelve compounds were tested against CDK2 and CDK1. Against CDK2, IC50 values were 51-100 nM (n=1), 11-50 nM (n=3) and 1-10 (n=8) and against CDK1 were greater than 100 (n=2), 51-100 nM (n=3), 11-50 nM (n=5) and 1-10 (n=2).

USE - Used for the treatment of diseases mediated by kinases such as abl, ATK, bcr-abl, Blk, Brk, Btk, c-kit, c-met, c-src, CDK1, CDK2, **CDK4**, CDK6, cRaf1, CSF1R, CSK, EGFT, ErbB2, ErbB3, ErbB4, ERK, Fak, fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, FLK-4, flt-1, Fps, Frk, Fyn, HCckk, IGF-1R, INS-R, Jak, KDR, Lck, Lyn, MEK, p38, PDGFFR, PIK, PJKC, PYJK2, ros, tie1, tie2, TRK, Yes and Zap70 as well as **cyclin -dependent kinases** (claimed). Used to treat organ transplant rejection, chemotherapy-induced alopecia or thrombocytopenia,

to **inhibit tumor** growth, and to treat mucositis, restenosis, atherosclerosis, rheumatoid arthritis, angiogenesis, hepatic cirrhosis, glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic angiopathy, glomerulopathy, psoriasis, diabetes mellitus, inflammation, neurodegenerative diseases, macular degeneration, actinic keratosis and hyperproliferative disorders (claimed). Also used for the treatment of viral or eukaryotic infections including those caused by cytomegalovirus and human papillomavirus.
Dwg.0/0

TECH UPTX: 19990609
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) are prepared by reacting 2-oxoindoline derivative of formula (II) with an aniline derivative of formula (III).

L20 ANSWER 23 OF 24 WPIDS (C) 2002 THOMSON DERWENT
AN 1996-040227 [04] WPIDS
CR 1998-321627 [28]
DNC C1996-013598
TI **Cyclin-dependent kinase-4** binding protein - used in the isolation of (ant)agonists of cell cycle regulation..
DC B04 D16
IN DRAETTA, G; GYURIS, J
PA (MITO-N) MITOTIX INC
CYC 21
PI WO 9533819 A2 19951214 (199604)* EN 115p
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: AU CA JP KR
AU 9526627 A 19960104 (199613)
WO 9533819 A3 19960321 (199630)
US 5691147 A 19971125 (199802) 62p
ADT WO 9533819 A2 WO 1995-US7113 19950602; AU 9526627 A AU 1995-26627 19950602; WO 9533819 A3 WO 1995-US7113 19950602; US 5691147 A US 1994-253155 19940602
FDT AU 9526627 A Based on WO 9533819
PRAI US 1994-253155 19940602
AB WO 9533819 A UPAB: 19980715
A novel substantially pure preparation of **cyclin-dependent kinase** (**CDK**)-**4** binding protein, or a fragment comprises an amino acid sequence at least 60% homologous to a polypeptide selected from one of 24 sequences given in the specification. Related nucleotide sequences, antibodies, vectors and host cells are also claimed.
USE - The **CDK4**-binding protein and CDK may be used in an assay for **screening** test compounds as inhibitors of an interaction of CDK with **CDK4**-binding protein, **CDK4**-binding protein fusion proteins may be used to identify agents which disrupt the ability of a **CDK4**-binding protein to regulate a eukaryotic cell cycle. The nucleic acids, or fragments of them may be used as primers in a method to determine the risk for a subject, of a disorder characterised by unwanted cell proliferation caused by the presence or absence or a genetic lesion in a gene encoding one of the 24 polypeptide sequences (all claimed) as **CDK4** and D-type cyclins are strongly implicated in the control of cell proliferation during the GI phase and are strong candidates for oncogenes that could be major factors in tumourigenesis.
Dwg.0/1

L20 ANSWER 24 OF 24 WPIDS (C) 2002 THOMSON DERWENT
AN 1995-131101 [17] WPIDS

CR 1993-214192 [26]; 1996-020353 [02]; 1996-230371 [23]
DNN N1995-103061 DNC C1995-060503
TI Nucleic acid encoding a protein or polypeptide that inhibits DNA synthesis in a recipient cell - useful to inhibit cell proliferation in tumour cells, treat wound or burn tissue, or as an antiviral or antiparasitic agent.
DC B04 D16 S03
IN SMITH, J R; KAY, B K
PA (BAYU) BAYLOR COLLEGE MEDICINE; (UYNC-N) UNIV NORTH CAROLINA
CYC 21
PI WO 9506415 A1 19950309 (199517)* EN 169p
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: AU CA JP US
AU 9476760 A 19950322 (199527)
AU 9526444 A 19951218 (199611)
EP 723402 A1 19960731 (199635) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
JP 09502094 W 19970304 (199719) 171p
AU 692794 B 19980618 (199835)
EP 723402 A4 19971217 (199840)
ADT WO 9506415 A1 WO 1994-US9700 19940826; AU 9476760 A AU 1994-76760 19940826; AU 9526444 A AU 1995-26444 19950523; EP 723402 A1 EP 1994-927257 19940826, WO 1994-US9700 19940826; JP 09502094 W WO 1994-US9700 19940826, JP 1995-508203 19940826; AU 692794 B AU 1994-76760 19940826; EP 723402 A4 EP 1994-927257 19940826
FDT AU 9476760 A Based on WO 9506415; AU 9526444 A Based on WO 9531995; EP 723402 A1 Based on WO 9506415; JP 09502094 W Based on WO 9506415; AU 692794 B Previous Publ. AU 9476760, Based on WO 9506415
PRAI US 1994-274535 19940713; US 1993-113372 19930830; US 1993-153564 19931117; US 1994-160814 19940103; US 1994-203535 19940225; US 1994-229420 19940415; US 1994-268439 19940630; US 1994-249371 19940524; US 1994-321814 19941003; US 1994-327874 19941024
AB WO 9506415 A UPAB: 19981021
Purified nucleic acid (NA) encodes a protein or polypeptide that inhibits DNA synthesis in a recipient cell. Also claimed are (1) an oligonucleotide with at least 19 bases, which hybridises to the complement of a given 2106 bp sequence; (2) an oligonucleotide capable of inhibiting the expression of SDI-1 by formn. of a triplex structure, which comprises only G and C and is at least 20 bases long, and which hybridises at a region of the ds molecule that is at least 65% purine or pyrimidine, where the oligonucleotide has a G where a complementary location on the SDI-1-encoding NA is a GC base pair and a T where the complementary location has an AT base pair; (3) a purified antagonist of a protein or polypeptide capable of: (a) inhibiting DNA synthesis in a recipient cell, and (b) associating with a cyclin or **cyclin-dependent kinase**; (4) an antibody (Ab) capable of binding SDI-1; (5) a purified protein or polypeptide capable of: (a) inhibiting DNA synthesis in a recipient cell, and (b) associating with a cyclin or **cyclin-dependent kinase**; (6) an analogue of the protein of (5) which also has functions (a) and (b); (7) method of repressing inhibition of DNA synthesis in a quiescent or senescent human cell by providing to the cell a NA with a sequence complementary to an RNA encoding a protein which inhibits DNA synthesis, where the NA hybridises with the RNA; and (8) a method for direct delivery of an agent into a target cell by: (a) conjugating the agent to SDI or a fragment capable of being transported into the target cell, and (b) incubating the conjugated molecule with the target cell to permit transport into the cell.
USE - The SDI-1 protein and NA are useful for inhibiting DNA synthesis and cell proliferation in tumour cells. They may also be used on in vitro cultured cells. The protein or NA may be administered with a

chemotherapeutic, antiviral or antimicrobial agent. The NA of (7) is useful for treating wound or burn tissue, and permits angiogenesis to occur. It may be contacted with skin cells ex vivo and cultured to form progeny cells that are reintroduced to the patient. It may also be used to produce an immortalised cell line which produce a biological cpd. The Ab is useful for determining the presence or concn. of SDI-1 in a sample. The molecules may also be used as antiviral or antiparasitic agents, or may be given as an adjunct to antiviral agents to synchronise the cell cycles of virally infected cells.
Dwg.0/6

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=> fil biosis
FILE 'BIOSIS' ENTERED AT 08:13:56 ON 20 MAY 2002
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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 15 May 2002 (20020515/ED)


=> d his

     (FILE 'BIOSIS' ENTERED AT 08:08:18 ON 20 MAY 2002)
               DEL HIS Y
L1          1936 S CDK4 OR CDK 4 OR CYCLIN DEPENDENT KINASE (2W) 4
L2         10880 S C MYC
L3            76 S L1 (L) L2
L4        164964 S SCREEN?
L5             0 S L3 AND L4
L6           461 S L1 (4A) INHIBIT?
L7            13 S L3 AND L6
L8          7642 S BURKITT#
L9             3 S L3 AND L8
L10       255855 S ANTICANCER# OR ANTITUMOR# OR ANTI (2A) (CANCER OR TUMOR OR NE
L11            8 S L3 AND L10
L12        19290 S NEUROBLASTOM?
L13          161 S 8 (2W) 14(2W) TRANSLOC?
L14            1 S L12 AND L3
L15            0 S L13 AND L3
L16         1163 S MUTAT? (3A) (APC OR CATENIN)
L17            0 S L16 AND L3
L18           22 S L7 OR L9 OR L11 OR L14

     FILE 'BIOSIS' ENTERED AT 08:13:56 ON 20 MAY 2002

=> d bib ab it 1-22

L18  ANSWER 1 OF 22  BIOSIS  COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN   2002:129826  BIOSIS
DN   PREV200200129826
TI   Acceleration of G1 cooperates with CBFbeta-SMMHC to induce acute leukemia
     in mice.
AU   Friedman, Alan D. (1); Yang, Yandan (1); Wang, Weihua (1); Cheng, Linzhao
     (1); Civin, Curt I. (1)
CS   (1) Pediatric Oncology, Johns Hopkins University, Baltimore, MD USA
SO   Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 93a-94a.
     http://www.bloodjournal.org/. print.
     Meeting Info.: 43rd Annual Meeting of the American Society of Hematology,
     Part 1 Orlando, Florida, USA December 07-11, 2001
     ISSN: 0006-4971.
DT   Conference
LA   English
AB   CBFbeta-SMMHC is expressed from an inv16 or t(16;16) chromosome in 8% of
     AML patients. This oncoprotein sequesters CBFalpha subunits, including
     AML1 (RUNX1), in multimers which form via its Smooth Muscle Myosin Heavy
     Chain domain. Core Binding Factor (CBF) activities are also reduced in
     other subsets of AML: 5% harbor point mutations in the AML1 gene, and 12%
     express AML1-ETO from the t(8;21) chromosome. AML1-ETO binds to CBF cisDNA
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elements and represses transcription. TEL-AML1, expressed in 25% of pediatric B-lineage ALLs, acts similarly. Reduction of CBF-mediated trans-activation both blocks differentiation and delays progression from G1 to S. In cell lines, **cdk4**, cyclin D2, or **c-Myc** overcomes the evident cell cycle inhibition. We therefore sought to determine whether acceleration of G1 would cooperate with CBFbeta-SMMHC in vivo. We created CRE-packaging lines producing retroviral vectors expressing CBFbeta-SMMHC, E7, both, or neither. E7 is a viral protein which stimulates G1 by inactivating Rb. Analysis of viral RNAs from CRE supernatants showed that the CBFbeta-SMMHC/E7 titre was 2-fold lower than the other vectors. Unfractionated marrow cells from C57BL/6 mice treated with 5-FU were co-cultured with irradiated packaging lines with IL-3, IL-6, SCF, and polybrene for 48 hrs. 2 million cells were then injected IV into syngeneic recipients which had been irradiated to 9.5 Gy. After 17 months, 0 of 20 mice receiving the empty MING vector developed leukemia, 2 of 18 CBFbeta-SMMHC mice developed leukemia at 13 or 15 months, 2 of 18 E7 mice developed leukemia at 7.5 or 8 months, and 8 of 30 CBFbeta-SMMHC/E7 mice developed leukemia at a mean of 5.8 months. Six of the CBFbeta-SMMHC/E7 mice developed leukemia at least 2 months earlier than the E7 mice - the hazard ratio for CBFbeta-SMMHC/E7 versus E7 was 3.0, even though the CBFbeta-SMMHC/E7 vector had a lower titre. As another means to accelerate G1, we transduced the MING or CBFbeta-SMMHC vectors into marrow isolated from mice lacking the over-lapping p16INK4a and p19ARF genes. Within the first 7 months, 4 of 16 CBFbeta-SMMHC/p16p19 mice developed leukemia, whereas 0 of 17 MING/p16p19 mice have done so. Genomic southern blot analysis identified the CBFbeta-SMMHC DNA in two of the four CBFbeta-SMMHC/E7 leukemias analyzed, whereas only about 6% of Sca+ marrow cells were transduced by the corresponding vector. Lack of detection in 2 leukemias may reflect technical limitations or that CBFbeta-SMMHC was required to initiate but not to maintain transformation. All of the leukemias obtained were T-lineage ALL except for three B-ALLs and one AML. Two million cells from four CBFbeta-SMMHC/E7 mice were transplanted into syngeneic, non-irradiated recipients, and each gave rise to secondary leukemias after 1 to 2 months. TCR-Vbeta subset analysis of five T-ALLs demonstrated that each was clonal. As chimeric CBFbeta-SMMHC mice treated with the mutagen ENU develop AML, we transplanted additional groups of mice with wild-type marrow transduced with the MING or CBFbeta-SMMHC vectors and injected them with 50 mg/kg ENU intraperitoneally 35 days later. 5 of 9 CBFbeta-SMMHC mice developed T-ALL at a mean age of 4.5 months, and after 7 months 2 of 16 MING/ENU mice have developed leukemia, at 5.5 and 6 months. Perhaps the MSCV LTR in our vector biases expression to the T-lineage. Nevertheless, our findings support a model in which mutations that accelerate G1 potentiate the ability of CBF oncoproteins or AML1 mutations to contribute to leukemogenesis by inhibiting differentiation and perhaps apoptosis. In AML, inactivation of the p15 promoter or **c-myc** over-expression may serve this role.

IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Immune System (Chemical Coordination and Homeostasis); Tumor Biology

IT Parts, Structures, & Systems of Organisms
bone marrow cell: blood and lymphatics, immune system

IT Diseases
acute leukemia: blood and lymphatic disease, etiology, immune system disease, neoplastic disease

IT Chemicals & Biochemicals
5-FU [5-fluorouracil]: **antineoplastic** - drug; CBF-beta-SMMHC: expression; CBF-beta-SMMHC DNA: expression; E7: expression; IL-3 [interleukin-3]; IL-6 [interleukin-6]; SCF [stem cell factor]; polybrene

IT Alternate Indexing

Leukemia (MeSH)
IT Miscellaneous Descriptors
G1 acceleration; cell cycle: C1 phase; Meeting Abstract; Meeting Poster
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Retroviridae: Animal Viruses, Viruses, Microorganisms
ORGN Organism Name
C57BL/6 mouse (Muridae); retrovirus (Retroviridae): gene vector
ORGN Organism Superterms
Animal Viruses; Animals; Chordates; Mammals; Microorganisms; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates; Viruses
RN 51-21-8 (5-FLUOROURACIL)
28728-55-4 (POLYBRENE)

L18 ANSWER 2 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:397469 BIOSIS
DN PREV200100397469
TI Inhibitory effects of 1alpha,25-dihydroxyvitamin D3 on the G1-S phase-controlling machinery.
AU Jensen, Simon Skjode (1); Madsen, Mogens Winkel; Lukas, Jiri; Binderup, Lise; Bartek, Jiri
CS (1) Department of Molecular Biology and Biochemistry, Leo Pharmaceutical Products, Industriparken 55, Ballerup, 2750 Denmark
SO Molecular Endocrinology, (August, 2001) Vol. 15, No. 8, pp. 1370-1380. print.
ISSN: 0888-8809.
DT Article
LA English
SL English
AB The nuclear hormone 1alpha,25-dihydroxyvitamin D3 induces cell cycle arrest, differentiation, or apoptosis depending on target cell type and state. Although the antiproliferative effect of 1alpha,25-dihydroxyvitamin D3 has been known for years, the molecular basis of the cell cycle blockade by 1alpha,25-dihydroxyvitamin D3 remains largely unknown. Here we have investigated the mechanisms underlying the G1 arrest induced upon 1alpha,25-dihydroxyvitamin D3 treatment of the human breast cancer cell line MCF-7. Twenty-four-hour exposure of exponentially growing MCF-7 cells to 1alpha,25-dihydroxyvitamin D3 impeded proliferation by preventing S phase entry, an effect that correlated with appearance of the growth-suppressing, hypophosphorylated form of the retinoblastoma protein (pRb), and modulation of cyclin-dependent kinase (cdk) activities of **cdk-4**, -6, and -2. Time course immunochemical and biochemical analyses of the cellular and molecular effects of 1alpha,25-dihydroxyvitamin D3 treatment for up to 6 d revealed a dynamic chain of events, preventing activation of cyclin D1/**cdk4**, and loss of cyclin D3, which collectively lead to repression of the E2F transcription factors and thus negatively affected cyclin A protein expression. While the observed 10-fold **inhibition** of cyclin D1/**cdk 4**-associated kinase activity appeared independent of cdk inhibitors, the activity of cdk 2 decreased about 20-fold, reflecting joint effects of the lower abundance of its cyclin partners and a significant increase of the cdk inhibitor p21CIP1/WAF1, which blocked the remaining cyclin A(E)/cdk 2 complexes. Together with a rapid down-modulation of the **c-Myc** oncoprotein in response to 1alpha,25-dihydroxyvitamin D3, these results demonstrate that 1alpha,25-dihydroxyvitamin D3 inhibits cell proliferation by targeting several key regulators governing the G1/S transition.
IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Cell Biology; Endocrine System (Chemical Coordination and Homeostasis)

IT Diseases
breast cancer: neoplastic disease, reproductive system disease/female
IT Chemicals & Biochemicals
1-alpha,25-dihydroxyvitamin D-3: inhibitory effects, nuclear hormone; **c-Myc**: down-modulation, oncoprotein; cyclin A: expression; cyclin-dependent kinase-2 [cdk-2]; **cyclin-dependent kinase-4 [cdk-4**]; cyclin-dependent kinase-6 [cdk-6]
IT Alternate Indexing
Breast Neoplasms (MeSH)
IT Miscellaneous Descriptors
G-1-S phase-controlling machinery; apoptosis; cell cycle; cell differentiation
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
MCF-7 cell line (Hominidae): human breast cancer cells
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates
RN 141349-86-2 (CYCLIN-DEPENDENT KINASE-2)
147014-97-9 (CYCLIN-DEPENDENT KINASE-4)
154907-66-1 (CYCLIN-DEPENDENT KINASE-6)

L18 ANSWER 3 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:312618 BIOSIS
DN PREV200100312618
TI Analysis of the expression of cell cycle regulators in Ewing cell lines: EWS-FLI-1 modulates p57KIP2 and c-Myc expression.
AU Dauphinot, Luce; De Oliveira, Catherine; Melot, Thomas; Sevenet, Nicolas; Thomas, Venetia; Weissman, Bernard E.; Delattre, Olivier (1)
CS (1) Laboratoire de Pathologie Moleculaire des Cancers, INSERM U509, Institut Curie, 26 Rue d'Ulm, 75248, Paris Cedex 05 France
SO Oncogene, (31 May, 2001) Vol. 20, No. 25, pp. 3258-3265. print. ISSN: 0950-9232.
DT Article
LA English
SL English
AB Ewing tumour is characterized by specific chromosome translocations which fuse EWS to a subset of genes encoding ETS transcription factors, most frequently FLI-1. We report the analysis of the expression of various cell cycle regulators both in Ewing tumour derived cell lines and in different cellular models with either inducible or constitutive EWS-FLI-1 cDNA expression. In Ewing cell lines, cyclin D1, **CDK4**, Rb, p27KIP1 and **c-Myc** were consistently highly expressed whereas p57KIP2, p15INK4B and p14ARF demonstrated undetectable or low expression levels. The amount of p16INK4A, p21CIP1, p18INKAC and CDK6 was variable from one cell line to the other. The inducible expression of EWS-FLI-1 led to a strong upregulation of **c-Myc** and a considerable downregulation of p57KIP2. Other proteins did not show evident modification. High **c-Myc** and very low p57KIP2 expression levels were also observed in **neuroblastoma** NGP cells constitutively expressing EWS-FLI-1 as compared to parental cells. Analysis of the p57KIP2 promoter indicated that EWS-FLI-1 downregulates, possibly through an indirect mechanism, the transcription of this gene. Finally, we show that ectopic expression of p57KIP2 in Ewing cells blocks proliferation through a complete G1 arrest. These results suggest that the modulation of p57KIP2 expression by EWS-FLI-1 is a fundamental step in Ewing tumorigenesis.
IT Major Concepts
Molecular Genetics (Biochemistry and Molecular Biophysics); Tumor

Biology
IT Diseases
Ewing tumor: neoplastic disease
IT Chemicals & Biochemicals
CDK4; EWS-FLI-1; Rb; **c-Myc**; cDNA [complementary DNA]; cyclin D1; p14-ARF; p15-INK4B; p16; p18; p21; p27-KIP1; p57-KIP2
IT Miscellaneous Descriptors
G1 arrest; cell cycle: regulation; chromosome translocations
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
A673 cell line (Hominidae): human Ewing's tumor cells; EW-3 cell line (Hominidae): human Ewing's tumor cells; EW1 cell line (Hominidae): human Ewing's tumor cells; EW16 cell line (Hominidae): human Ewing's tumor cells; EW17 cell line (Hominidae): human Ewing's tumor cells; EW24 cell line (Hominidae): human Ewing's tumor cells; EW7 cell line (Hominidae): human Ewing's tumor cells; ICB104 cell line (Hominidae): human Ewing's tumor cells; LAP35 cell line (Hominidae): human Ewing's tumor cells; ORS cell line (Hominidae): human Ewing's tumor cells; Poe cell line (Hominidae): human Ewing's tumor cells; RDES-1 cell line (Hominidae): human Ewing's tumor cells; SKES-1 cell line (Hominidae): human Ewing's tumor cells
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates

L18 ANSWER 4 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:182411 BIOSIS
DN PREV200100182411
TI **Antitumor** protein (AP) from a mushroom induced apoptosis to transformed human keratinocyte by controlling the status of pRb, c-MYC, cyclin E-cdk2, and p21WAF1 in the G1/S transition.
AU Kawamura, Yukio (1); Manabe, Mariko (1); Kitta, Kazumi (1)
CS (1) National Food Research Institute, 2-1-2 Kannon-dai, Tsukuba, Ibaraki, 305-8642 Japan
SO Biofactors, (2000) Vol. 12, No. 1-4, pp. 157-160. print.
ISSN: 0951-6433.
DT Article
LA English
SL English
AB **Antitumor** protein (AP) from a mushroom, induced the morphological changes typical to apoptosis such as nuclear condensation, aneuploidity, and DNA fragmentation at concentrations as low as 5-20 ng/ml to cancer cells. Molecular alterations related to cell cycle. Molecular alterations related to cell cycle, especially G1/S transition were investigated with a human keratinocyte transformed with oncoproteins, E6 and E7 of human pappiloma virus(HPV)-16. AP didn't alter significantly and oncosuppressor p53 level, but induced hyperphosphorylation of pRb. Time-dependent change of G1 cyclins, cdk2 and cdk4 after addition of AP showed that expression level of cdk inhibitors, INK4 family, and p27KIP1 did not altered, while that of p21WAF1 was downregulated.
IT Major Concepts
Cell Biology; Pharmacognosy (Pharmacology)
IT Parts, Structures, & Systems of Organisms
keratinocyte: integumentary system, transformed
IT Chemicals & Biochemicals
INK4; **antitumor** protein; **c-MYC**; cdk2 [cyclin-dependent kinase 2]; **cdk4** [**cyclin-dependent kinase 4**]; cyclin E; p21-WAF1; p27-KIP1; p53; pRb [retinoblastoma protein]

IT Miscellaneous Descriptors
G1/S cell transition; apoptosis: induction; cell cycle; cellular viability
ORGN Super Taxa
Basidiomycetes: Fungi, Plantae; Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
A31 cell line (Hominidae); SV-T2 cell line (Muridae); mushroom (Basidiomycetes)
ORGN Organism Superterms
Animals; Chordates; Fungi; Humans; Mammals; Microorganisms; Nonhuman Mammals; Nonhuman Vertebrates; Nonvascular Plants; Plants; Primates; Rodents; Vertebrates
RN 141349-86-2 (CYCLIN-DEPENDENT KINASE 2)
147014-97-9 (CYCLIN-DEPENDENT KINASE 4)

L18 ANSWER 5 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:124682 BIOSIS
DN PREV200100124682
TI Targeted inactivation of the p21WAF1/cip1 gene enhances Apc-initiated tumor formation and the tumor-promoting activity of a Western-style high-risk diet by altering cell maturation in the intestinal mucosa.
AU Yang, Wan Cai; Mathew, Joseph; Velcich, Anna; Edelmann, Winfried; Kucherlapati, Raju; Lipkin, Martin; Yang, Kan; Augenlicht, Leonard H. (1)
CS (1) Department of Oncology, Albert Einstein Cancer Center, Montefiore Hospital, 111 East 210th Street, Bronx, NY, 10467: augen@aecom.yu.edu USA
SO Cancer Research, (January 15, 2001) Vol. 61, No. 2, pp. 565-569. print. ISSN: 0008-5472.
DT Article
LA English
SL English
AB Elimination of both alleles of the gene that encodes the cyclin kinase inhibitor p21WAF1/cip1 increases the frequency and size of intestinal tumors in Apc1638+/- mice that inherit a mutant allele of the Apc gene, and intermediate effects are seen if a single p21 allele is inactivated. The increased tumor formation is associated with altered cell maturation in the intestinal mucosa of the p21-deficient mice-increased cell proliferation, and decreased apoptosis, and goblet cell differentiation-that is also a function of p21 gene dosage. Moreover, a Western-style diet that mimics principal risk factors for colon cancer (high fat and phosphate, low calcium and vitamin D) accelerates tumor formation in Apc1638+/- mice, and the loss of a single or both p21 alleles is additive with the tumor-promoting effects of this diet, resulting in more and larger tumors, and a highly significant decrease in survival time. Thus, p21 normally suppresses Apc-initiated tumor formation and is haplo-insufficient in this regard. This is consistent with recent reports that Apc initiates tumor formation by up-regulating **c-myc** expression through altered beta-catenin-Tcf signaling and that **c-myc** then up-regulates **cdk4**, whose activity is **inhibited** by p21. Decreased expression of p21 is also a marker of poor prognosis in patients, and the data presented suggest that dietary alterations in patients undergoing treatment for colon cancer might be highly effective in improving outcome.
IT Major Concepts
Molecular Genetics (Biochemistry and Molecular Biophysics); Nutrition; Tumor Biology
IT Diseases
colon cancer: digestive system disease, neoplastic disease, tumor development

IT Alternate Indexing
Colonic Neoplasms (MeSH)
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mouse (Muridae): animal model
ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates
GEN mouse adenomatous polyposis coli gene [mouse Apc gene] (Muridae): Western style high-risk diet effects, tumor formation initiating activity, tumor promoting activity; mouse p21-WAF-1-cip-1 gene (Muridae): targeted inactivation, tumor development role

L18 ANSWER 6 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2000:435488 BIOSIS
DN PREV200000435488
TI Effects of the red wine constituent resveratrol on the colon carcinoma cell line Caco-2.
AU Wolter, F. (1); Akoglu, B. (1); Caspary, W. F. (1); Stein, J. (1)
CS (1) 2nd Dept. of Medicine, J. W. Goethe University, Frankfurt Germany
SO Clinical Nutrition (Edinburgh), (August, 2000) Vol. 19, No. Supplement 1, pp. 25-26. print.
Meeting Info.: 22nd Congress of the European Society of Parenteral and Enteral Nutrition Madrid, Spain September 09-13, 2000
ISSN: 0261-5614.
DT Conference
LA English
SL English
IT Major Concepts
Cell Biology; Pharmacognosy (Pharmacology); Tumor Biology
IT Chemicals & Biochemicals
CDK4: expression; PCNA [proliferating cell nuclear antigen]: expression; **c-myc**: expression; cyclin D1: expression; cyclin E: expression; pRB: expression; resveratrol: **antineoplastic** - drug, red wine constituent
IT Methods & Equipment
Western blot: analytical method, gene mapping; flow cytometry: analytical method, cytophotometry: CB, cytophotometry: CT
IT Miscellaneous Descriptors
G1/S-phase; G2/M phase; apoptosis; cell cycle; cell growth; cell proliferation; red wine: alcoholic beverage; Meeting Abstract
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Caco-2 cell line (Hominidae): human colon carcinoma cells
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates
RN 501-36-0 (RESVERATROL)

L18 ANSWER 7 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2000:429802 BIOSIS
DN PREV200000429802
TI Cell cycle activation by c-myc in a **Burkitt** lymphoma model cell line.
AU Pajic, Alexander; Spitkovsky, Dimitry; Christoph, Barbara; Kempkes, Bettina; Schuhmacher, Marino; Staege, Martin S.; Brielmeier, Markus; Ellwart, Joachim; Kohlhuber, Franz; Bornkamm, Georg W.; Polack, Axel; Eick, Dirk (1)
CS (1) GSF-Research Center for Environment and Health, Marchioninistrasse 25,

D-81377, Munich Germany
SO International Journal of Cancer, (15 September, 2000) Vol. 87, No. 6, pp. 787-793. print.
ISSN: 0020-7136.
DT Article
LA English
SL English
AB The product of the proto-oncogene **c-myc** (myc) is a potent activator of cell proliferation. In **Burkitt** lymphoma (BL), a human B-cell tumor, myc is consistently found to be transcriptionally activated by chromosomal translocation. The mechanisms by which myc promotes cell cycle progression in B-cells is not known. As a model for myc activation in BL cells, we have established a human EBV-EBNA1 positive B-cell line, P493-6, in which myc is expressed under the control of a tetracycline regulated promoter. If the expression of myc is switched off, P493-6 cells arrest in G0/G1 in the presence of serum. Re-expression of myc activates the cell cycle without inducing apoptosis. myc triggers the expression of cyclin D2, cyclin E and **Cdk4**, followed by the activation of cyclin E-associated kinase and hyper-phosphorylation of Rb. The transcription factor E2F-1 is expressed in proliferating and arrested cells at constant levels. The Cdk inhibitors p16, p21, p27 and p57 are expressed at low or not detectable levels in proliferating cells and are not induced after repression of myc. Ectopic expression of p16 inhibits cell cycle progression. These data suggest that myc triggers proliferation of P493-6 cells by promoting the expression of a set of cell cycle activators but not by inactivating cell cycle inhibitors.
IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology
IT Parts, Structures, & Systems of Organisms
B-cells: blood and lymphatics, immune system
IT Diseases
Burkitt lymphoma: blood and lymphatic disease, immune system disease, neoplastic disease
IT Chemicals & Biochemicals
Cdk-4: expression; Rb: hyperphosphorylation; **c-myc**: cell cycle activation; cyclin D-2: expression; cyclin E: expression; cyclin E-associated kinase: activation; p16: Cdk inhibitor, expression; p21: Cdk inhibitor, expression; p27: Cdk inhibitor, expression; p57: Cdk inhibitor, expression; human **c-myc** gene (Hominidae): expression, proto-oncogene
IT Alternate Indexing
Burkitt Lymphoma (MeSH)
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
P493-6 cell line (Hominidae)
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates

L18 ANSWER 8 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2000:313550 BIOSIS
DN PREV200000313550
TI Stem cell factor inhibits erythroid differentiation by modulating the activity of G1-cyclin-dependent kinase complexes: A role for p27 in erythroid differentiation coupled G1 arrest.
AU Tamir, Ami; Petrocelli, Teresa; Stetler, Kendra; Chu, Wendy; Howard, Jeff; St. Croix, Brad; Slingerland, Joyce; Ben-David, Yaacov (1)
CS (1) Department of Medical Biophysics, University of Toronto, 2075 Bayview Avenue, S-216, Toronto, ON, M4N 3M5 Canada

SO Cell Growth & Differentiation, (May, 2000) Vol. 11, No. 5, pp. 269-277. print.
ISSN: 1044-9523.
DT Article
LA English
SL English
AB Terminal erythroid differentiation is accompanied by decreased expression of c-Kit and decreased proliferation of erythroid progenitor cells. Using a newly established erythroleukemia cell line HB60-5, which proliferates in response to erythropoietin (Epo) and stem cell factor (SCF) and differentiates when stimulated with Epo alone, we characterized several events associated with the cell cycle during erythroid differentiation. Forty-eight h after SCF withdrawal and Epo stimulation, there was strong **inhibition** of **cyclin-dependent kinase** (**cdk**) **4** and cdk6 activities, associated with an increase in the binding of p27 and p15 to cdk6. A significant increase in the binding of p27 to cyclin E- and cyclin A-associated cdk2 correlated with the inhibition of these kinases. In addition, the expression of **c-Myc** and its downstream transcriptional target Cdc25A were found to be down-regulated during Epo-induced terminal differentiation of HB60-5 cells. The loss of Cdc25A was associated with an increase in the phosphotyrosylation of cyclin E-associated cdk2, which may contribute to cell cycle arrest during differentiation. Although overexpression of p27 in HB60-5 cells caused G1 arrest, it did not promote terminal erythroid differentiation. Thus, the cell cycle arrest that involves p27 is part of a broader molecular program during HB60-5 erythroid differentiation. Moreover, we suggest that SCF stimulation of erythroblasts, in addition to inhibiting erythroid differentiation, activates parallel or sequential signals responsible for maintaining cyclin/cdk activity.
IT Major Concepts
Biochemistry and Molecular Biophysics
IT Parts, Structures, & Systems of Organisms
erythroblasts: blood and lymphatics; erythroid: blood and lymphatics; erythroid progenitor cell: blood and lymphatics
IT Chemicals & Biochemicals
G1-cyclin-dependent kinase; cdk2; cdk4; cdk6; cyclin-dependent kinase; p27; stem cell factor
RN 150428-23-2 (CYCLIN-DEPENDENT KINASE)

L18 ANSWER 9 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2000:224637 BIOSIS
DN PREV200000224637
TI Retinoic acid induces persistent, RARalpha-mediated anti-proliferative responses in Epstein-Barr virus-immortalized B lymphoblasts carrying an activated c-myc oncogene but not in **Burkitt**'s lymphoma cell lines.
AU Cariati, Roberta; Zancai, Paola; Quaia, Michele; Cutrona, Giovanna; Giannini, Franca; Rizzo, Silvana; Boiocchi, Mauro (1); Dolcetti, Riccardo
CS (1) Division of Experimental Oncology 1, Centro di Riferimento Oncologico, via Pedemontana Occidentale 12, I-33081, Aviano Italy
SO International Journal of Cancer, (May 1, 2000) Vol. 86, No. 3, pp. 375-384.
ISSN: 0020-7136.
DT Article
LA English
SL English
AB We have previously demonstrated that 13-cis-retinoic acid (RA), 9-cis-RA and all-trans-RA (ATRA) powerfully inhibit the proliferation of Epstein-Barr virus-immortalized B-lymphoblastoid cell lines (LCLs). The

aim of the present study was to assess whether these compounds are effective at inhibiting the growth of B cells at more advanced stages of lymphomagenesis, including fully transformed B lymphocytes. To this end, **c-myc**-transfected LCLs (myc-LCLs) and **Burkitt**
's lymphoma (BL) cell lines were used. We report that 13-cis-RA, 9-cis-RA and ATRA also markedly inhibit the proliferation of myc-LCLs by inducing G0/G1 growth arrest as well as enhancing rates of apoptosis. Conversely, all but I (DG75) of the 8 BL cell lines investigated were poorly RA-responsive. Moreover, unlike LCLs and myc-LCLs, RA-treated DG75 cells rapidly resumed proliferation upon drug removal. Analysis of cell cycle-regulatory proteins showed that, as in LCLs, strong up-regulation of p27Kip-I and increased levels of under-phosphorylated pRb and p130 were detected in RA-treated DG75 cells. While the catalytic activity of all 3 G1-associated CDKs (CDK2, **CDK4** and CDK6) was strongly
inhibited in RA-treated LCLs, only CDK2-associated kinase activity was reduced in DG75 cells arrested in G0/G1 by RA. Moreover, RA-treated DG75 cells failed to show the down-regulation of cyclin D3 observed in LCLs. Use of receptor-selective agonists and antagonists showed that in LCLs and RA-responsive BL cells, RA-induced growth arrest is mainly mediated by RARalpha. The RARalpha-selective agonist Ro 40-6055 was also effective at very low concentrations (10-10 M). Nevertheless, comparable levels of RARalpha mRNA were found in RA-responsive and -resistant BL cell lines, indicating that mechanisms different from transcriptional deregulation of RARalpha probably underlie the differential responsiveness of BL cells.

IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Tumor Biology
IT Parts, Structures, & Systems of Organisms
B cells: blood and lymphatics, immune system; B lymphoblasts: Epstein-Barr virus-immortalized cell lines, blood and lymphatics, immune system
IT Diseases
Burkitt's lymphoma: blood and lymphatic disease, cell ines, immune system disease, neoplastic disease, viral disease
IT Chemicals & Biochemicals
all-trans retinoic acid; retinoic acid; retinoic acid receptor-alpha; c-myc gene (Muridae): oncogene
IT Alternate Indexing
Burkitt Lymphoma (MeSH)
IT Miscellaneous Descriptors
lymphomagenesis
ORGN Super Taxa
Herpesviridae: Animal Viruses, Viruses, Microorganisms
ORGN Organism Name
Epstein-Barr virus (Herpesviridae)
ORGN Organism Superterms
Animal Viruses; Microorganisms; Viruses
RN 302-79-4 (ALL-TRANS RETINOIC ACID)
302-79-4 (RETINOIC ACID)

L18 ANSWER 10 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2000:69909 BIOSIS
DN PREV200000069909
TI Antiproliferative function of p27kip1 is frequently inhibited in highly malignant **Burkitt**'s lymphoma cells.
AU Barnouin, Karin; Fredersdorf, Steffen; Eddaoudi, Ayad; Mittnacht, Sibylle; Pan, Lang Xing; Du, Ming Qin; Lu, Xin (1)
CS (1) Ludwig Institute for Cancer Research, Imperial College School of Medicine at St. Mary's, Norfolk Place, London, W2 1PG UK
SO Oncogene, (Nov. 4, 1999) Vol. 18, No. 46, pp. 6388-6397.

ISSN: 0950-9232.
DT Article
LA English
SL English
AB Lack of detectable expression of p27kip1 cyclin dependent kinase inhibitor has previously been correlated with high degree of malignancy in human breast, colorectal, gastric and small cell lung carcinomas. Here we demonstrate that an inverse correlation between p27kip1 expression and tumour malignancy also exists in most types of human B cell lymphomas examined. A clear exception was **Burkitt**'s lymphoma (BL), a highly malignant tumour which often expresses high levels of p27kip1. Analysis of p27kip1 derived from **Burkitt**'s lymphoma cell lines expressing high levels of p27kip1, BL40 and BL41, in a cyclin E/cdk2 kinase inhibition assay demonstrated that p27kip1 is not permanently inactivated since heat treatment can restore the inhibitory activity of p27kip1. However, p27kip1 expressed in these two cell lines is largely sequestered in inactive complexes and we have no evidence that **c-myc** or Epstein-Barr virus are responsible for the sequestration of p27kip1 in these two cell lines although **c-myc** and EBV are two oncogenic agents often associated with **Burkitt**'s lymphomas. Interestingly, we observed that high level p27kip1 expression often correlated with cyclin D3 overexpression both in vivo and in BL cell lines. The majority of p27kip1 in BL40 cells was complexed with cyclin D3 indicating that overexpressed cyclin D3 may at least be part of the sequestering activity for the inhibitory function of p27kip1. Furthermore, cyclinD3/**cdk4** complex could sequester p27kip1 in a cyclin E/cdk2 kinase assay in vitro. Finally, we show that cyclin D3 transfected into an inducible p27kip1 cell line could overcome the G1 arrest mediated by p27kip1. These results argue that in addition to down-regulation of p27kip1 expression, some tumour cells can sequester and tolerate the antiproliferative function of p27kip1. They also suggest a novel role for the overexpression of D-type cyclins as one pathway allowing tumour cells to overcome the antiproliferative function of p27kip1.
IT Major Concepts
Tumor Biology
IT Chemicals & Biochemicals
p27-kip-1 protein: antiproliferative function inhibition, tumor cell expression
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
BL-40 cell line (Hominidae): human **Burkitt** lymphoma cell line; BL-41 cell line (Hominidae): human **Burkitt** lymphoma cell line
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates

L18 ANSWER 11 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1999:489009 BIOSIS
DN PREV199900489009
TI Vitamin K3 induces cell cycle arrest and cell death by inhibiting Cdc25 phosphatase.
AU Wu, F.Y.-H.; Sun, T.-P. (1)
CS (1) Division of Cancer Research, Institute of Biomedical Sciences, Academia Sinica, Taipei, 115 Taiwan
SO European Journal of Cancer, (Sept., 1999) Vol. 35, No. 9, pp. 1388-1393. ISSN: 0959-8049.
DT Article
LA English
SL English

AB Our early reports have indicated that vitamin K3 (VK3) exerts antitumour activity by inhibiting Cdk1 activity and overexpressing the **c-myc** gene to induce an apoptotic cell death. In the present study, we investigated the effect of VK3 on Cdc25 phosphatase, a Cdk1 activator and **c-Myc**-downstream protein. Increased protein level but decreased activity of Cdc25A phosphatase was found in cervical carcinoma SiHa cells treated with VK3 for 1 h and allowed to recover for 8, 24, 30 or 45 h. The binding of VK3 to Cdc25 phosphatase was proven by incubating (methyl-3H)-VK3 with the 27 kDa-catalytic domain of Cdc25A phosphatase at 35degreeC for 2 h. We found that VK3 inhibited cyclin E expression at late G1 phase and cyclin A at G1/S transition of the aphidicolin-synchronised SiHa cells, but had no effect on Cdk2 and **Cdk4**. The **inhibition** of cyclins E and A expression was associated with cell cycle progression delay in the S phase. These results indicate that binding of VK3 to the catalyticdomain of Cdc25 phosphatase results in the formation of inactive, hyperphosphorylated Cdk1 that subsequently induces cell cycle arrest, leading to cell death. These findings suggest a possible therapeutic strategy, with VK3 serving as a potential antagonist to tumours expressing high levels of proteins containing cysteine such as oncogenic Cdc25A phosphatase.

IT Major Concepts
Gynecology (Human Medicine, Medical Sciences); Oncology (Human Medicine, Medical Sciences); Pharmacology

IT Diseases
cervical carcinoma: neoplastic disease, reproductive system disease/female

IT Chemicals & Biochemicals
cyclin A: expression, inhibition; cyclin E: expression, inhibition; cysteine: expression; tritiated-methyl vitamin K3; vitamin K3: **antineoplastic** - drug, vitamin - drug; Cdc25 phosphatase: Cdk1 activator, **c-Myc**-downstream protein, activity, inhibition, expression; Cdk1: expression, hyperphosphorylation; Cdk2: expression; **Cdk4**: expression

IT Alternate Indexing
Carcinoma (MeSH); Cervix Neoplasms (MeSH)

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
human (Hominidae); SiHa cell line (Hominidae): cell cycle arrest, cell death, cervical carcinoma cell line

ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates

RN 140208-22-6 (CDC25 PHOSPHATASE)
52-90-4Q (CYSTEINE)
3374-22-9Q (CYSTEINE)
58-27-5 (VITAMIN K3)

L18 ANSWER 12 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1999:431403 BIOSIS
DN PREV199900431403
TI Myc downregulation by transforming growth factor beta required for activation of the p15Ink4b G1 arrest pathway.
AU Warner, Beverley J.; Blain, Stacy W.; Seoane, Joan; Massague, Joan (1)
CS (1) Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021 USA
SO Molecular and Cellular Biology, (Sept., 1999) Vol. 19, No. 9, pp. 5913-5922.
ISSN: 0270-7306.
DT Article
LA English

SL English
AB The antimitogenic action of transforming growth factor beta (TGF-beta) in epithelial cells involves cyclin-dependent kinase (cdk) inhibitory gene responses and downregulation of **c-Myc** expression. Although the cdk inhibitory responses are sufficient for G1 arrest, enforced expression of **c-Myc** prevents G1 arrest by TGF-beta. We investigated the basis of this antagonism by using Mv1Lu lung epithelial cell lines that conditionally express levels of human **c-Myc**. We show that **c-Myc** prevents induction of the **cdk4 inhibitor** p15Ink4b and the subsequent inhibition of G1 cdks by TGF-beta. We assessed the significance of this effect by analyzing the oligomeric state of **cdk4** in these cells. In proliferating cells, endogenous **cdk4** is distributed among three populations: an abundant high-molecular-mass (>400-kDa) pool of latent **cdk4** that serves as a source of **cdk4** for cyclin D, a low-abundance pool containing active cyclin D-**cdk4** complexes, and an inactive population of monomeric **cdk4**. Cell stimulation with TGF-beta converts the latent and active **cdk4** pools into inactive **cdk4**, an effect that is specifically mimicked by overexpression of p15 but not by other forms of G1 arrest. This process of TGF-beta-induced **cdk4** inactivation is completely blocked by expression of **c-Myc**, even though the latent and active **cdk4** complexes from **c-Myc**-expressing cells remain sensitive to dissociation by p15 in vitro. **c-Myc** causes a small increase in cyclin D levels, but this effect contributes little to the loss of TGF-beta responses in these cells. The evidence suggests that **c-Myc** interferes with TGF-beta activation of the p15 G1 arrest pathway. TGF-beta must therefore downregulate **c-Myc** in order to activate this pathway.
IT Major Concepts
Cell Biology; Enzymology (Biochemistry and Molecular Biophysics)
IT Chemicals & Biochemicals
c-Myc: regulation; cyclin D; **cyclin-dependent kinase 4**; p15-Ink4b; transforming growth factor-beta
IT Miscellaneous Descriptors
cell cycle
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Mustelidae: Carnivora, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae); Mv1Lu cell line (Mustelidae)
ORGN Organism Superterms
Animals; Carnivores; Chordates; Humans; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Primates; Vertebrates
RN 147014-97-9 (CYCLIN-DEPENDENT KINASE 4)

L18 ANSWER 13 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1999:300004 BIOSIS
DN PREV199900300004
TI Mysterious liaisons: The relationship between c-Myc and the cell cycle.
AU Obaya, Alvaro J.; Mateyak, Maria K.; Sedivy, John M. (1)
CS (1) Department of Molecular Biology, Cell Biology and Biochemistry, Brown University, Providence, RI, 02912 USA
SO Oncogene, (May 13, 1999) Vol. 18, No. 19, pp. 2934-2941. ISSN: 0950-9232.
DT General Review
LA English
SL English

AB A large body of physiological evidence shows that either upregulation or downregulation of intracellular **c-Myc** activity has profound consequences on cell cycle progression. Recent work suggests that **c-Myc** may stimulate the activity of cyclin E/cyclin-dependent kinase 2 (Cdk2) complexes and antagonize the action of the Cdk **inhibitor** p27KIP1. Cyclin D/**Cdk4**/6 complexes have also been implicated as targets of **c-Myc** activity. However, in spite of considerable effort, the mechanisms by which **c-Myc** interacts with the intrinsic cyclin/Cdk cell cycle machinery remain undefined.

IT Major Concepts
Cell Biology; Molecular Genetics (Biochemistry and Molecular Biophysics)

IT Chemicals & Biochemicals
c-Myc gene (Animalia): cell cycle relationship, cyclin E-cyclin-dependent kinase 2 complex stimulation

ORGN Super Taxa
Animalia

ORGN Organism Name
animal (Animalia): animal model

ORGN Organism Superterms
Animals

RN 9031-44-1 (KINASE)

L18 ANSWER 14 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

AN 1999:283282 BIOSIS

DN PREV199900283282

TI Apoptosis and growth inhibition in malignant lymphocytes after treatment with arsenic trioxide at clinically achievable concentrations.

AU Zhu, Xin-Hua; Shen, Yu-Lei; Jing, Yong-kui; Cai, Xun; Jia, Pei-Ming; Huang, Ying; Tang, Wei; Shi, Gui-Ying; Sun, Yue-Ping; Dai, Jie; Wang, Zhen-Yi; Chen, Sai-Juan; Zhang, Ting-Dong; Waxman, Samuel; Chen, Zhu; Chen, Guo-Qiang (1)

CS (1) Shanghai Institute of Hematology, Rui-Jin Hospital, Shanghai Second Medical University, 197 Rui-Jin Rd. II, Shanghai, 200025 China

SO Journal of the National Cancer Institute (Bethesda), (May 5, 1999) Vol. 91, No. 9, pp. 772-778.
ISSN: 0027-8874.

DT Article

LA English

SL English

AB Background: Arsenic trioxide (As2O3) can induce clinical remission in patients with acute promyelocytic leukemia via induction of differentiation and programmed cell death (apoptosis). We investigated the effects of As2O3 on a panel of malignant lymphocytes to determine whether growth-inhibitory and apoptotic effects of As2O3 can be observed in these cells at clinically achievable concentrations. Methods: Eight malignant lymphocytic cell lines and primary cultures of lymphocytic leukemia and lymphoma cells were treated with As2O3, with or without dithiothreitol (DTT) or buthionine sulfoximine (BSO) (an inhibitor of glutathione synthesis). Apoptosis was assessed by cell morphology, flow cytometry, annexin V protein level, and terminal deoxynucleotidyl transferase labeling of DNA fragments. Cellular proliferation was determined by 5-bromo-2'-deoxy-uridine incorporation into DNA and flow cytometry and by use of a mitotic arrest assay. Mitochondrial transmembrane potential (DELTAPSIm) was measured by means of rhodamine 123 staining and flow cytometry. Protein expression was assessed by western blot analysis or immunofluorescence. Results: Therapeutic concentrations of As2O3 (1-2 muM) had dual effects on malignant lymphocytes: 1) inhibition of growth through adenosine triphosphate (ATP) depletion and prolongation of cell cycle time

and 2) induction of apoptosis. As2O3-induced apoptosis was preceded by DELTAPSIm collapse. DTT antagonized and BSO enhanced As2O3-induced ATP depletion, DELTAPSIm collapse, and apoptosis. Caspase-3 activation, usually resulting from DELTAPSIm collapse, was not always associated with As2O3-induced apoptosis. As2O3 induced PML (promyelocytic leukemia) protein degradation but did not modulate expression of cell cycle-related proteins, including **c-myc**, retinoblastoma protein, **cyclin-dependent kinase 4**, cyclin D1, and p53, or expression of differentiation-related antigens. Conclusions: Substantial growth inhibition and apoptosiswithout evidence of differentiation were induced in most malignant lymphocytic cells treated with 1-2 muM As2O3. As2O3 may prove useful in the treatment of malignant lymphoproliferative disorders.

IT Major Concepts
Hematology (Human Medicine, Medical Sciences); Oncology (Human Medicine, Medical Sciences); Pharmacology

IT Diseases
lymphocytic leukemia: blood and lymphatic disease, immune system disease, neoplastic disease; lymphoma: blood and lymphatic disease, immune system disease, neoplastic disease

IT Chemicals & Biochemicals
arsenic trioxide: **antineoplastic** - drug; butathione sulfoximine: **antineoplastic** - drug; dithiothreitol: **antineoplastic** - drug

IT Alternate Indexing
Leukemia, Lymphocytic (MeSH); Lymphoma (MeSH)

IT Miscellaneous Descriptors
apoptosis

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
human (Hominidae): patient

ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates

RN 1327-53-3 (ARSENIC TRIOXIDE)
3483-12-3 (DITHIOTHREITOL)
14616-60-5 (SULFOXIMINE)

L18 ANSWER 15 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:507478 BIOSIS
DN PREV199800507478
TI A novel function of adenovirus E1A is required to overcome growth arrest by the CDK2 inhibitor p27Kip1.
AU Alevizopoulos, Konstantinos; Catarin, Barbara; Vlach, Jaromir; Amati, Bruno (1)
CS (1) Swiss Inst. Exp. Cancer Res., CH-1066 Epalinges Switzerland
SO EMBO (European Molecular Biology Organization) Journal, (Oct. 15, 1998) Vol. 17, No. 20, pp. 5987-5997.
ISSN: 0261-4189.
DT Article
LA English
AB We show here that the adenovirus E1A oncoprotein prevents growth arrest by the CDK2 inhibitor p27Kip1 (p27) in rodent fibroblasts. However, E1A neither binds p27 nor prevents inhibition of CDK2 complexes in vivo. In contrast, the amount of free p27 available to inhibit cyclin E/CDK2 is increased in E1A-expressing cells, owing to reduced expression of cyclins D1 and D3. Moreover, E1A allows cell proliferation in the presence of supraphysiological p27 levels, while **c-Myc**, known to induce a cellular p27-inhibitory activity, is only effective against physiological p27 concentrations. E1A also bypasses G1 arrest by

roscovitine, a chemical inhibitor of CDK2. Altogether, these findings imply that E1A can act downstream of p27 and CDK2. Retinoblastoma (pRb)-family proteins are known CDK substrates; as expected, association of E1A with these proteins (but not with p300/CBP) is required for E1A to prevent growth arrest by either p27 or the **CDK4**/6 **inhibitor** p16INK4a. Bypassing CDK2 inhibition requires an additional function of E1A: the mutant E1A DELTA26-35 does not overcome p27-induced arrest, while it binds pRb-family proteins, prevents p16-induced arrest, and alleviates pRb-mediated repression of E2F-1 transcriptional activity (although E1A DELTA26-35 fails to restore expression of E2F-regulated genes in p27-arrested cells). We propose that besides the pRb family, E1A targets specific effector(s) of CDK2 in G1-S control.

IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology
IT Parts, Structures, & Systems of Organisms
fibroblasts
IT Chemicals & Biochemicals
p27-Kip1: CDK2 inhibitor; retinoblastoma-family proteins
IT Miscellaneous Descriptors
cell cycle control; cell proliferation; growth arrest
ORGN Super Taxa
Adenoviridae: Animal Viruses, Viruses, Microorganisms; Rodentia: Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
adenovirus E1A (Adenoviridae); rodent (Rodentia)
ORGN Organism Superterms
Animal Viruses; Animals; Chordates; Mammals; Microorganisms; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates; Viruses

L18 ANSWER 16 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:404510 BIOSIS
DN PREV199800404510
TI c-Myc-enhanced S phase entry in keratinocytes is associated with positive and negative effects on cyclin-dependent kinases.
AU Alexandrow, Mark G.; Moses, Harold L. (1)
CS (1) Dep. Cell Biol., Vanderbilt Univ. Sch. Med., Nashville, TN 37232-6838 USA
SO Journal of Cellular Biochemistry, (Sept. 15, 1998) Vol. 70, No. 4, pp. 528-542.
ISSN: 0730-2312.
DT Article
LA English
AB The function of the **c-myc** proto-oncogene in cell cycle progression remains unclear. In order to examine the role **c-myc** may play in cell cycle progression, we have expressed the hormone-inducible MycER protein in the nontransformed, EGF-dependent mouse keratinocyte cell line BALB/MK. We have found that activation of MycER, but not a mutant MycER, Gal4ER, or FosER, leads to an EGF-dependent and hormone-dependent increased incorporation of labeled thymidine only during the S phase of the cell cycle in BALB/MK cells. A possible explanation for the increase in thymidine incorporation comes from flow cytometric analyses that reveal that activation of MycER leads to an increase in the total number of cells that enter S phase after EGF restimulation. Investigation of the intracellular effects of Myc activation shows that the expression of several putative Myc-sensitive proteins, cyclins A, E, and D1, and the E2F-1 protein are unaffected by Myc induction. Interestingly, we find that the histone H1 kinase activity associated with an E2F-1 complex containing Cyclin A and Cdk-2, but not that associated with Cyclin E, in late G1 and early S phases is increased in cells

containing hormone-activated MycER, but not FosER. Although the mechanism for this Myc-dependent effect on E2F-1-associated kinase activity is still unknown, it does not appear to involve dissociation of the Cdk inhibitor p27Kip1 from the complexes as suggested by others. However, we have also found that hormone-treated cells actually show more p16INK4A **inhibitor** associated with another kinase, **Cdk-4** , as the cells are entering S phase. Altogether, the data suggest that the presence of excessive Myc protein in keratinocytes can stimulate otherwise noncycling cells to enter the cell cycle, and that this effect of Myc involves both positive effects on E2F-1-associated Cdk-2 and negative effects on **Cdk-4** in late G1.

IT Major Concepts
Cell Biology; Molecular Genetics (Biochemistry and Molecular Biophysics)
IT Chemicals & Biochemicals
c-myc gene: proto-oncogene; cyclin-dependent kinase
IT Miscellaneous Descriptors
cell cycle: S phase entry; cell proliferation
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
BALB/MK (Muridae)
ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates
RN 9031-44-1D (KINASES)
9031-44-1 (KINASE)

L18 ANSWER 17 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:205740 BIOSIS
DN PREV199800205740
TI Myc and the cell cycle.
AU Amati, Bruno (1); Alevizopoulos, Konstantinos; Vlach, Jaromir
CS (1) Swiss Inst. Exp. Cancer Res., CH-1066 Epalinges Switzerland
SO Frontiers in Bioscience, (Feb. 15, 1998) Vol. 3, No. CITED FEB. 24, 1998, pp. D250-268. http://www.bioscience.org/1998/v3/d/trosko/d208-236.htm http://www.bioscience.org/1998/v3/d/trosko/d208-236.htm. MRK06263/17/98.
DT General Review
LA English
AB Ectopic expression of the **c-Myc** oncoprotein prevents cell cycle arrest in response to growth-inhibitory signals, differentiation stimuli, or mitogen withdrawal. Moreover, Myc activation in quiescent cells is sufficient to induce cell cycle entry in the absence of growth factors. Thus, Myc transduces a potent mitogenic stimulus but, concomitantly, induces apoptosis in the absence of survival factors. We review here recent progress in our understanding of the molecular mechanisms linking Myc activity to cell cycle control. Myc is a positive regulator of G1-specific cyclin-dependent kinases (CDKs) and, in particular, of cyclin E/CDK2 complexes. Cyclin D/**CDK4** and CDK6 may conceivably also be activated by Myc, but the circumstances in which this occurs remain to be explored. Myc acts via at least three distinct pathways which can enhance CDK function: (1) functional inactivation of the CDK inhibitor p27Kip1 and probably also of p21Cip1 and p57Kip2, (2) induction of the CDK-activating phosphatase Cdc25A and (3) - in an ill understood and most likely indirect way - deregulation of cyclin E expression. Constitutive expression of either Myc or cyclin E can prevent growth arrest by p16INK4a (an **inhibitor** of cyclin D/**CDK4** , but not of cyclin E/CDK2). In cells, p16INK4a inhibits phosphorylation, and thus induces activation of the Retinoblastoma-family proteins (pRb, p107 and p130). Surprisingly, this effect of p16 is not altered in the

presence of Myc or cyclin E. Thus, Myc and cyclin E/CDK2 activity unlink activation of p16 and pRb from growth arrest. Finally, Myc may itself be a functional target of cyclin D/**CDK4** through its direct interaction with p107. We discuss how the effects of Myc on cell cycle control may relate to its oncogenic activity, and in particular to its ability to cooperate with activated Ras oncoproteins.

IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology

IT Chemicals & Biochemicals
cdc25A; cyclin D1; cyclin E: expression; oncogenes; p27Kip1; tumor suppressors; Myc; Ras

IT Miscellaneous Descriptors
cell cycle control; cell growth; cellular transformation; mitogenic signaling

ORGN Super Taxa
Mammalia: Vertebrata, Chordata, Animalia

ORGN Organism Name
mammal (Mammalia)

ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Vertebrates

L18 ANSWER 18 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1997:112827 BIOSIS
DN PREV199799412030
TI Cyclic AMP negatively controls **c-myc** transcription and G1 cell cycle progression in p210 BCR-ABL transformed cells: Inhibitor activity exerted through cyclin D1 and **cdk4**.
AU Williamson, E. A.; Burgess, G. S.; Eder, P.; Litz-Jackson, S.; Boswell, H. Scott
CS IB 442, 975 W. Walnut St., Indianapolis, IN USA
SO Leukemia (Basingstoke), (1997) Vol. 11, No. 1, pp. 73-85. ISSN: 0887-6924.
DT Article
LA English
AB Raised intracellular cyclic AMP (cAMP) has been demonstrated to exert an antiproliferative effect in myeloid cells. How the antiproliferative activity of cAMP is exerted in p210 BCR-ABL transformed myeloid cells was the subject of this investigation. It was hypothesized that **cyclin dependent kinase 4**, **cdk4**, might be a critical target enzyme to affect the related events of **c-myc** transcription and progression through G1 phase of the cell cycle within cells transformed by p210 BCR-ABL, and further, that **cdk4** might be downregulated by cAMP to inhibit proliferation. In order to investigate the regulatory role of **cdk4**, synchronized cells were studied. In p210 BCR-ABL transformed cells transiting early G1 phase, treatment with a cAMP analogue led to inhibition of cyclin D1 synthesis, and marked reduction of **cdk4** kinase activity. Within cells in which **cdk4** was **inhibited** by cAMP, there was augmented interaction of E2F1 with the retinoblastoma protein, pRb in a nuclear matrix-associated cell fraction. As a result of E2F1 sequestration, raised intracellular cAMP was found to inhibit **c-myc** transcription in p210 BCR-ABL transformed myeloid cells synchronously transiting the early G1 phase of the cell cycle. A target of this transcriptional suppression exerted by cAMP was the E2F site of the **c-myc** P2 promoter. On the other hand, cyclin D1 content was not reduced by cAMP in these cells when it was applied at a later cell cycle stage at the interface between G1 and S. Corresponding to lack of cyclin D1 inhibition in these later G1-to-S phase cells, **cdk4** activity was only modestly suppressed, and **c-myc** mRNA

expression was also inhibited to a lesser degree. These studies show that Rb interaction with E2F1 is regulated by **cdk4** and cyclin D1 within p210 BCR-ABL transformed leukemia cells in early G1 phase of the cell cycle. In this context, both cyclin D1 and **cdk4** are subject to the level of intracellular cAMP. This interaction between Rb and E2F1, which is subject to the level of cAMP, is critical to transcriptional control of **c-myc**. Further, pRb regulation of E2F activity affects cellular potential for G1-S phase transition in p210 BCR-ABL transformed myeloid cells, in part, via its effect on **c-myc** transcription.

IT Major Concepts
Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); Development; Enzymology (Biochemistry and Molecular Biophysics); Genetics; Tumor Biology

IT Chemicals & Biochemicals
CYCLIC AMP

IT Miscellaneous Descriptors
BLOOD AND LYMPHATICS; **C-MYC**; **CDK4**; CYCLIC AMP; CYCLIN D1; **CYCLIN-DEPENDENT KINASE 4**; EXPRESSION; E2F1; G1 CELL CYCLE PROGRESSION; MESSENGER RNA; MRNA; MYELOID CELLS; PRB; P210 BCR-ABL; P210 BCR-ABL-TRANSFORMED; RETINOBLASTOMA PROTEIN; SYNTHESIS; TRANSCRIPTION; TUMOR BIOLOGY

RN 60-92-4 (CYCLIC AMP)

L18 ANSWER 19 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1997:30917 BIOSIS
DN PREV199799337320
TI P21-ras-mediated decrease of the retinoblastoma protein in fibroblasts occurs through growth factor-dependent mechanisms.
AU Kivinen, Laura; Tiihonen, Erja; Haapajarvi, Tarja; Laiho, Marikki (1)
CS (1) Haartman Inst., Dep. Virology, Univ. Helsinki, P.O. Box 21, FIN-00014 Helsinki Finland
SO Cell Growth & Differentiation, (1996) Vol. 7, No. 12, pp. 1705-1712. ISSN: 1044-9523.
DT Article
LA English
AB Stable coexpression of the human retinoblastoma protein (pRB) cDNA and EJ c-Ha-ras oncogene in murine fibroblasts leads to loss of pRB expression with concomitant transformation of the cells (1). We show here that conditional expression of p21-ras in mouse fibroblasts expressing human pRB leads to a rapid decrease of pRB expression at both protein and mRNA levels. The decrease of pRB mRNA is blocked by cycloheximide, suggesting the requirement of ongoing protein synthesis. p21-ras expression leads also to decreases of **c-myc** and tissue metalloproteinase **inhibitor**-2 mRNAs, whereas **cyclin-dependent kinase 4**, cyclin D1, E2F-1, and ornithine decarboxylase are unaffected. The decrease in pRB is accompanied by progressive morphological transformation of the cells. The effect of p21-ras on pRB expression was serum and growth factor dependent. A shift of the cells to low serum (0.2% FCS) abolished the effects of p21-ras on pRB, but this effect was reconstituted by the addition of growth factors epidermal growth factor, fibroblast growth factor-2, transforming growth factor beta-1, and platelet-derived growth factor to the cells. The results suggest a complex interaction between p21-ras, pRB, and growth factors in the control of cell growth. p21-ras appears to drive the cell cycle by deregulation of key cell cycle regulators, the functions of which in low serum become redundant or require the presence of growth factors positively driving the cell cycle.

IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Development;

Endocrine System (Chemical Coordination and Homeostasis); Genetics; Metabolism; Sense Organs (Sensory Reception); Skeletal System (Movement and Support); Tumor Biology

IT Miscellaneous Descriptors
CANCER; CELL CYCLE; CELL CYCLE REGULATORS; CELL DIFFERENTIATION; CELL GROWTH; EJ C-HA-RAS ONCOGENE; ENDOCRINE SYSTEM; EPIDERMAL GROWTH FACTOR; EXPRESSION; FIBROBLAST GROWTH FACTOR-2; FIBROBLASTS; GROWTH FACTOR; GROWTH FACTOR-DEPENDENT MECHANISMS; HUMAN RETINOBLASTOMA PROTEIN; HUMAN RETINOBLASTOMA PROTEIN CDNA; HUMAN RETINOBLASTOMA PROTEIN COMPLEMENTARY DNA; HUMAN RETINOBLASTOMA PROTEIN MESSENGER RNA; HUMAN RETINOBLASTOMA PROTEIN MRNA; NEOPLASTIC DISEASE; PLATELET-DERIVED GROWTH FACTOR; P21-RAS; P21-RAS-MEDIATED DECREASE; P21-RAS-MEDIATED RETINOBLASTOMA PROTEIN DECREASE; SKELETAL SYSTEM; TRANSFORMING GROWTH FACTOR-BETA-1

ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
murine (Muridae)

ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates

L18 ANSWER 20 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1996:79667 BIOSIS
DN PREV199698651802
TI Differential effects of retinoids and antiestrogens on cell cycle progression and cell cycle regulatory genes in human breast cancer cells.
AU Wilcken, Nicholas R. C.; Sarcevic, Boris; Musgrove, Elizabeth A.; Sutherland, Robert L. (1)
CS (1) Cancer Biol. Div., Garvan Inst. Med. Res., St. Vincent's Hosp., Darlinghurst, NSW 2010 Australia
SO Cell Growth & Differentiation, (1996) Vol. 7, No. 1, pp. 65-74. ISSN: 1044-9523.
DT Article
LA English
AB Retinoids have antiproliferative effects in human breast cancer cells and share some characteristics with antiestrogens, although the molecular targets involved have yet to be identified in either case. Using T-47D human breast cancer cells, we compared the effects of retinoic acid (RA) and the antiestrogen ICI 164384 on cell cycle phase distribution and the expression of genes with known functions in cell cycle control. Both RA and ICI 164384 inhibited cell cycle progression in G-1 phase, but the RA effect was delayed by 16 h. This delay in action was also seen with 9-cis RA and other retinoids. Administration of 17-beta-estradiol abolished the effects of ICI 164384 but was without effect in RA-treated cells. Antiestrogen treatment caused a rapid inhibition of **c-myc** and cyclin D1 gene expression and reduced Cdk2 activity by more than 50% at 24 h. RA, however, did not affect **c-myc** or cyclin D1 gene expression, nor did it significantly change the mRNA or protein levels of cyclins D3 or E or cyclin-dependent kinases (CDK) Cdk2 or **Cdk4**. RA-induced reduction in Cdk2 activity was modest and occurred after %S phase declined, while **Cdk4** activity was reduced, coincident with cell cycle changes. However, following either RA or ICI 164384, there was a reduction in the amount of hyperphosphorylated pRB, first apparent well before cell cycle changes were seen. These data demonstrate that: (a) the mechanisms of action of antiestrogens and retinoids are different but converge at pRB; and (b) RA can affect CDK activity without reducing cyclin or CDK levels.

IT Major Concepts
Cell Biology; Enzymology (Biochemistry and Molecular Biophysics);

Genetics; Oncology (Human Medicine, Medical Sciences); Pathology; Pharmacology; Reproductive System (Reproduction)
IT Chemicals & Biochemicals
RETINOIC ACID; ICI-164384; KINASE
IT Miscellaneous Descriptors
ANTINEOPLASTIC-DRUG; CANCER THERAPY; CYCLIN-DEPENDENT KINASE; CYCLINS; GENE EXPRESSION; ICI-164384; PHARMACODYNAMICS; RETINOIC ACID
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
T-47D (Hominidae): cell line
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN 302-79-4 (RETINOIC ACID)
98007-99-9 (ICI-164384)
9031-44-1 (KINASE)

L18 ANSWER 21 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1995:487904 BIOSIS
DN PREV199598502204
TI C-Myc and Cyclin D3 (CcnD3) genes are independent targets for glucocorticoid inhibition of lymphoid cell proliferation.
AU Rhee, Kunsoo; Bresnahan, Wade; Hirai, Aki; Hirai, Masashi; Thompson, E. Aubrey (1)
CS (1) Dep. Human Biological Chem. Genetics, Univ. Texas-Galveston, Med. Branch, Basic Sci. Building, Galveston, TX 77550-0645 USA
SO Cancer Research, (1995) Vol. 55, No. 18, pp. 4188-4195.
ISSN: 0008-5472.
DT Article
LA English
AB Glucocorticoids inhibit the expression of critical cell cycle-regulatory genes. The G, cyclin gene CcnD3, which encodes cyclin D3, is inhibited by dexamethasone in P1798 murine T lymphoma cells. Glucocorticoids also inhibit expression of the catalytic partner of cyclin D3, **Cdk4**. **Inhibition** of these two genes results in a decrease in the ability to phosphorylate the Rb-1 tumor suppressor gene product. Stable transformation with SV40 T antigen expression vectors prevents glucocorticoid-mediated cell cycle arrest, which is consistent with the conclusion that glucocorticoids inhibit Rb-1 phosphorylation. Overexpression of cyclin D3 suffices to restore Rb-kinase activity in glucocorticoid-treated cells. Nevertheless, overexpression of cyclin D3 does not prevent glucocorticoid inhibition of cell proliferation. Cells transformed with **Cdk4** expression vectors, with or without cyclin D3 expression vectors, also undergo G-0, arrest in the presence of dexamethasone. Glucocorticoids inhibit **c-Myc** expression in lymphoid cells, and transient expression of **c-Myc** protein attenuates the lytic response in glucocorticoid-treated human leukemia cells (R. Thulasi, D. V. Harbour, and E. B. Thompson, J. Biol. Chem., 268: 18306-16312, 1993). However, P1798 cells stably transfected with **c-Myc** expression vectors are sensitive to glucocorticoid-mediated G-0 arrest. Such transformants withdraw from the cell cycle when treated with dexamethasone. P1798 cells were transformed so as to express both **c-Myc** protein and cyclin D3 in the presence of glucocorticoids. These Myc/D3 cells continue to proliferate in the presence of dexamethasone, and virtually all of these cells are capable of entering S phase in the presence of the steroid. Rapid apoptotic cell death occurs when wild-type P1798 cells are treated with dexamethasone in serum-free medium. Myc-transformed and cyclin D3-transformed cells also die rapidly when treated with glucocorticoids in the absence of serum. T antigen transformants are

resistant to glucocorticoid-mediated apoptosis in serum-free medium. Double transformants that express both cyclin D3 and **c-Myc** are also resistant to apoptosis in the presence of dexamethasone. We conclude that inhibition of both CcnD3 and **c-Myc** genes is critical to glucocorticoid-mediated Go arrest. Furthermore, those genes that convey resistance to growth arrest also convey resistance to cell death.

IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Genetics; Metabolism; Pharmacology; Tumor Biology

IT Chemicals & Biochemicals
DEXAMETHASONE

IT Miscellaneous Descriptors
ANTINEOPLASTIC-DRUG; DEXAMETHASONE; HORMONE-DRUG; P-1798 T-LYMPHOMA CELLS

ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Papovaviridae: Viruses

ORGN Organism Name
mouse (Muridae); SV40 (Papovaviridae)

ORGN Organism Superterms
animals; chordates; mammals; microorganisms; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates; viruses

RN 50-02-2 (DEXAMETHASONE)

L18 ANSWER 22 OF 22 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

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TI A fumagillin derivative angiogenesis inhibitor, AGM-1470, inhibits activation of cyclin-dependent kinases and phosphorylation of retinoblastoma gene product but not protein tyrosyl phosphorylation or protooncogene expression in vascular endothelial cells.

AU Abe, Jun'ichi; Zhou, Wei; Takuwa, Noriko; Taguchi, Jun'ichi; Kurokawa, Kiyoshi; Kumada, Mamoru; Takuwa, Yoh (1)

CS (1) Dep. Cardiovascular Biol., Fac. Med., Univ. Tokyo, 7-3-1 Hongo Bunkyo-ku, Tokyo 113 Japan

SO Cancer Research, (1994) Vol. 54, No. 13, pp. 3407-3412. ISSN: 0008-5472.

DT Article

LA English

AB Fumagillin analogue AGM-1470 potently inhibits angiogenesis with a minimal toxicity in vivo and is expected to be of therapeutic use as a powerful **antitumor** agent (Ingber et al., Nature, 348: 555-557, 1990). In the present study, we have investigated the effects and the mechanism of action of AGM-1470 on cultured human umbilical vein endothelial cells. AGM-1470 acts directly on endothelial cells to inhibit growth factor-induced DNA synthesis, with half maximal and maximal effects obtained at approximately 2 times 10-10 and 5 times 10-9 m, respectively. AGM-1470 does not inhibit early G-1 mitogenic events, such as cellular protein tyrosyl phosphorylation or the expression of immediate early genes c-fos and **c-myc**, but potently inhibits phosphorylation of RB protein, a tumor suppressor retinoblastoma gene product. The later addition of AGM-1470 up to 3 h after the growth factor stimulation still exerts full inhibitory effects on both DNA synthesis and RB phosphorylation, suggesting that the major site of action of AGM-1470 is located relatively late in the G, phase. AGM-1470 inhibits growth factor-induced activation of candidate RB V cdc2 and cdk2 but fails to inhibit them directly in vitro. AGM-1470 completely abolishes the growth factor-induced mRNA expression of cdc2 and cyclin A and partially inhibits that of cyclin E but has little effect on the mRNA level of cdk2,

cdk4, or cyclin D1. These results indicate that angioinhibitory action of AGM-1470 involves suppression of mRNA expression of specific members of cdks and cyclins and of activation of both cdc2 and cdk2 V in endothelial cells.

IT Major Concepts
Cardiovascular System (Transport and Circulation); Cell Biology; Development; Enzymology (Biochemistry and Molecular Biophysics); Genetics; Metabolism; Molecular Genetics (Biochemistry and Molecular Biophysics); Oncology (Human Medicine, Medical Sciences); Pharmacology; Sense Organs (Sensory Reception)

IT Chemicals & Biochemicals
FUMAGILLIN; AGM-1470; KINASES

IT Miscellaneous Descriptors
ANTINEOPLASTIC-DRUG; CARDIOVASCULAR-DRUG; DNA SYNTHESIS INHIBITION; HUMAN UMBILICAL VEIN CELLS; MESSENGER RNA; O-CHLOROACETYLCARBAMOYLFUMAGILLOL

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
Hominidae (Hominidae)

ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

RN 23110-15-8D (FUMAGILLIN)
129298-91-5 (AGM-1470)
9031-44-1D (KINASES)